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19th ANNUAL

APRIL 1-4, 2024

Drug Discovery Chemistry

Optimizing Small Molecules for Tomorrow's Therapeutics

HILTON BAYFRONT | SAN DIEGO, CA & VIRTUAL

APRIL 1, 2024

- Targeting Transcription Factors
- Covalent Modifications & Induced Proximity
- Generative AI & Predictive Modeling
- **In-Person Short Courses** April 1 & 3

APRIL 2 - 3, 2024

- Degraders & Molecular Glues - Part 1
- Fragment-Based Drug Discovery
- AI/ML for Early Drug Discovery - Part 1
- Encoded Libraries for Drug Discovery
- Small Molecule Immuno-Modulators
- The Medicinal Chemistry-Pharmacology Interface

APRIL 3 - 4, 2024

- Degraders & Molecular Glues - Part 2
- Protein-Protein Interactions
- AI/ML for Early Drug Discovery - Part 2
- Oral Peptides & Macrocyclics
- RNA-Modulating Small Molecule Drugs

PLENARY KEYNOTES

Applications of SuFEx Click Chemistry for Drug Discovery and Chemical Biology

Barry Sharpless, PhD

Scripps Research Institute;

2022 and 2001 Nobel Laureate

Reimagining Druggability Using Chemoproteomic Platforms

Daniel Nomura, PhD

University of California, Berkeley

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Drug Discovery Chemistry

CONFERENCE AT-A-GLANCE

MONDAY, APRIL 1	TUESDAY, APRIL 2	WEDNESDAY, APRIL 3	THURSDAY, APRIL 4
Targeting Transcription Factors	Degraders & Molecular Glues - Part 1	Degraders & Molecular Glues - Part 2	
Covalent Modifications & Induced Proximity	Fragment-Based Drug Discovery	Protein-Protein Interactions	
Generative AI & Predictive Modeling	AI/ML for Early Drug Discovery - Part 1	AI/ML for Early Drug Discovery - Part 2	
Pre-Conference In-Person Dinner Short Courses*	Encoded Libraries for Drug Discovery	Oral Peptides & Macrocyclics	
	Small Molecule Immuno-Modulators	RNA-Modulating Small Molecule Drugs	
	The Medicinal Chemistry-Pharmacology Interface		
	In-Person Dinner Short Courses*		

Premium or Separate Registration Required

PLENARY KEYNOTES

TUESDAY, APRIL 2

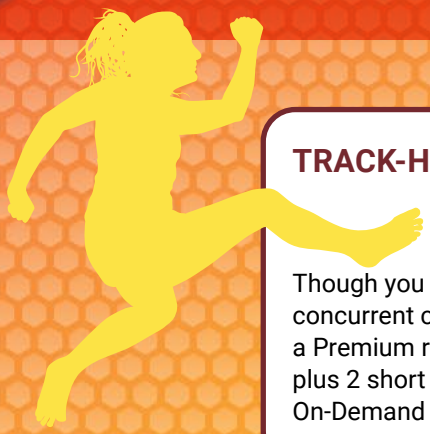
Applications of SuFEx Click Chemistry for Drug Discovery and Chemical Biology

Barry Sharpless, PhD, *Professor, Chemistry, Scripps Research Institute; 2022 and 2001 Nobel Laureate*

THURSDAY, APRIL 4

Reimagining Druggability Using Chemoproteomic Platforms

Daniel Nomura, PhD, *Professor of Chemical Biology and Molecular Therapeutics, Department of Chemistry, University of California, Berkeley*



TRACK-HOPPING

Attendees at Drug Discovery Chemistry are encouraged to "track-hop" between concurrent sessions:

Though you register for a particular conference, in reality you gain access to all concurrent conferences. For the best value and to best fit your research needs, select a Premium registration that gives you access to all 10 conferences, 3 symposia, plus 2 short courses over four days of programming. Your registration also includes On-Demand access for one year to access these concurrent conferences.

DINNER SHORT COURSES*

MONDAY, APRIL 1 6:00-8:30 PM

SC1: Protein Degraders: A Beyond Rule of Five Space and in vitro ADME Perspective

Instructor:

John Erve, PhD, President, Jerve Scientific Consulting

This course focuses on proteolysis targeting chimeras (PROTACs) and will cover topics relevant to developing them as oral therapeutics. Topics to be covered in this first part of the course will include their physicochemical properties and how these influence solubility and permeability and assays to determine polarity. We will also examine ADME topics focusing on *in vitro* assays including stability assays, transporters, drug-drug interactions (DDIs), Cytochrome P450 (CYP450) inhibition, etc.

SC2: Fragment-Based Drug Design: Advancing Tools and Technologies

Instructor:

Daniel A. Erlanson, PhD, Senior Vice President, Innovation and Discovery, Frontier Medicines Corporation

This course aims to introduce the fundamentals of Fragment-Based Lead Discovery (FBLD) to attendees. The first section will focus on the concepts of using fragments for hit generation. Special emphasis will be placed on practical pitfalls and the many ways to advance fragments to leads and drugs. The second part of the course will discuss the variety of fragment screening methods and when they are best applied. The composition of fragment libraries will also be discussed in detail. The attendees should come away from this course with a solid understanding of what FBLD is and how to apply it.

SC3: Fundamentals of Generative AI for Drug Discovery

Instructor:

Parthiban Srinivasan, PhD, Professor, Data Science and Engineering, Indian Institute of Science Education and Research, Bhopal

Deep generative modeling is rapidly transforming *de novo* drug discovery, streamlining the entire process. This course aims to explain the potential of AI, machine learning, and generative AI models in creating tailored molecules with specific properties. It explores the fundamentals of Variational Autoencoders (VAE), Generative Adversarial Networks (GAN), Transformers, Large Language Models (LLMs), BERT, and GPT models in the context of drug discovery, highlighting their crucial role in reshaping the pharmaceutical landscape. This course is designed for medicinal chemists, molecular modeling users, and project managers seeking to harness the capabilities of modern Generative AI concepts and integrate them into their work.

SC4: DNA-Encoded Libraries

Instructor:

Svetlana Belyanskaya, PhD, former Vice President, Biology, Anagenex

This course provides an overview of DNA-Encoded Library (DEL) screening platforms, discusses common selection strategies for identifying novel hits from DEL campaigns and delves into parameters for building a library collection. The instructors will also cover strategic considerations in using DEL selection data to accelerate hit-to-lead steps in drug discovery.

WEDNESDAY, APRIL 3 6:15-8:45 PM

SC5: Protein Degraders: An in vivo ADME and Safety Perspective

Instructor:

Donglu Zhang, PhD, Principal Scientist, Genentech Inc.

This course focuses on proteolysis targeting chimeras (PROTACs) and will cover topics relevant to developing them as therapeutics. Topics to be covered in this second part of the course will include looking at what is known about how PROTACs are metabolized *in vivo* and strategies to deliver them with adequate PK/PD. The unique mechanism of action of PROTACs gives rise to some drug safety issues not seen in small molecules, which will be discussed. Finally, we will explore the possible relevance of circadian rhythm to protein degradation and PROTACs.

SC6: Principles of Drug Design: Ligand-Receptor Interactions and More

Instructor:

Maricel Torrent, PhD, Principal Research Scientist, Computational Drug Discovery, AbbVie, Inc.

This course provides an overview of protein-ligand interactions and drug design principles. The presentation is targeted to medicinal chemists. The course starts by covering hydrophobic, H-bonding and electrostatic interactions. Then the course moves into coverage of specialized topics such as conformation analysis, pi-stack, cation-pi, halogen bonding, protein-protein interface, and covalent inhibition. Medicinal chemistry case studies are incorporated.

SC7: Chemical Biology for Covalent Discovery, Phenotypic Screening, and Target Deconvolution

Instructor:

Paul Brennan, PhD, Professor, Nuffield Department of Medicine, University of Oxford

This course is designed to provide an overview and best practices in the use of chemical biology probes and assays that have been developed for applications in early drug discovery. Chemists and biologists working in lead generation, assay development, phenotypic screening, target discovery and deconvolution, target engagement, and mechanism-of-action (MoA) studies will all benefit from attending this course. The instructors will share their knowledge and expertise around the use of various technologies and chemistries, and there will be time for open discussion and exchange of ideas.

**Premium or Separate Registration Required*

Short courses take place in-person only

SPONSORSHIP & EXHIBIT OPPORTUNITIES

CHI offers comprehensive packages that can be customized to your budget and objectives. Sponsorship allows you to achieve your goals before, during, and long after the event. Packages may include presentations, exhibit space and branding, as well as the use of delegate lists. Signing on early will maximize your exposure to qualified decision-makers and drive traffic to your website in the coming months.

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CHI will set up 6-8 in-person meetings during the conference, based on your selections from the advance registration list. Our staff will handle invites, confirmations and reminders, and walk the guest over to the meeting area. This package also includes a meeting space at the venue, complimentary main-conference registrations, branding, an 8'x10' exhibit space, and more.

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Exhibitors will enjoy facilitated networking opportunities with qualified delegates, making it the perfect platform to launch a new product, collect feedback, and generate new leads. Exhibit space sells out quickly, so reserve yours today!

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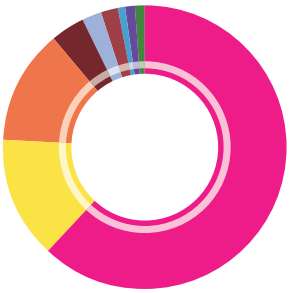
2023 ATTENDEE DEMOGRAPHICS

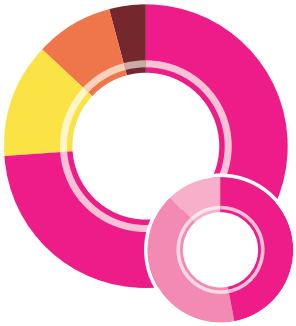
COMPANY TYPE

Biotech	62%
Pharma	14%
Academic	13%
Services	4%
Healthcare	2%
Other	2%
Government	1%
CRO	1%
Financial	1%



GEOGRAPHIC LOCATION

USA	74%
Europe	13%
Asia	9%
Rest of World	4%

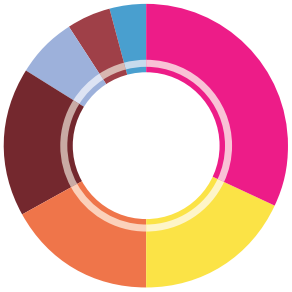


US Breakdown

West Coast	47%
East Coast	41%
Midwest	12%

DELEGATE TITLE

Scientist/Technologist	32%
Director	18%
Executive	17%
Sales & Marketing	17%
Professor	7%
Assistant	5%
Manager	4%



Reach Delegates from These

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AbbVie Inc, Dir Cancer Biology

Amgen Inc, Sr Principal Scientist, Drug Metabolism & Pharmacokinetics

Astex Pharmaceuticals Ltd, Sr Dir Computational Chemistry & Informatics

AstraZeneca, Sr Dir Medicinal Chemistry

Bayer LifeHub, Site Head of Chemical Biology, Precision Molecular Oncology

Baylor College of Medicine, Michael E DeBakey MD Prof, Pharmacology & Chemical Biology

Boehringer Ingelheim Pharma GmbH & Co KG, Head of Lab, Medicinal Chemistry

Brigham & Womens Hospital, Research Fellow, Cardiology

Bristol Myers Squibb, Sr Principal Scientist, Targeted Protein Degradation

Chugai Pharmaceutical Co Ltd, Medicinal Chemist, Discovery Chemistry

Dana Farber Cancer Institute, Assoc Prof, Biological Chemistry & Molecular Pharmacology

Dracen Pharmaceuticals, Head, Discovery Chemistry

Eli Lilly & Co, Dir Discovery Chemistry

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FDA CDER, Chemist, CDER & OPQ & OLDP

Genentech Inc, Dir & Principal Scientist, Biochemical & Cellular Pharmacology

Gilead Sciences Inc, Sr Research Scientist, Medicinal Chemistry

GSK, Dir Analytics

Janssen Pharmaceuticals Inc, Sr Dir & Site Head, Discovery Chemistry La Jolla

Johnson & Johnson Pharmaceutical R&D, Scientific Dir Computer Aided Drug Discovery

MD Anderson Cancer Ctr, Institute Research Investigator, Institute of Applied Cancer Sciences

Merck, Exec Dir Screening & Compound Profiling

Mitsubishi Tanabe Pharma Corp, Medicinal Chemistry, R&D

Natl Cancer Ctr, Prof, Cancer Biomedical Science

NIH NCATS, Scientific Program Mgr, Ofc of Special Initiatives

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Yuhan Corp, Principal Scientist, Drug Discovery Team II

Targeting Transcription Factors

Tools, Strategies, Modulators to Pursue Intrinsically Disordered Proteins

MONDAY, APRIL 1

12:00 pm Pre-Conference Symposium Registration

1:00 Welcome Remarks

1:10 Chairperson's Remarks

Stephen W. Fesik, PhD, Professor of Biochemistry, Pharmacology & Chemistry; Orrin H. Ingram II Chair in Cancer Research, Vanderbilt University

1:15 Overview of Intrinsic Challenges Drugging Transcription Factors

Stephen W. Fesik, PhD, Professor of Biochemistry, Pharmacology & Chemistry; Orrin H. Ingram II Chair in Cancer Research, Vanderbilt University

Transcription factors would be excellent targets for drug discovery in a variety of therapeutic areas except that they lack pockets suitable for tight binding to small molecules. In this session, approaches for overcoming these limitations will be presented, along with examples of targeting key transcription factors involved in disease.

1:25 AceTAC, a Novel, Innovative, and Targeted Protein Acetylation Modality

Md Shamiul Kabir, PhD, Postdoctoral Fellow, Laboratory of Dr. Jian Jin, Department of Pharmacological and Oncological Sciences, Icahn School of Medicine at Mount Sinai

Pharmacologic activation of tumor-suppressor proteins for cancer treatment remains a major challenge. We present a novel Acetylation Targeting Chimera (AceTAC) strategy to activate the p53 tumor suppressor protein via acetylation. We discovered and characterized the first p53Y220C AceTAC, MS78, which acetylated p53Y220C lysine 382 (K382) and suppressed proliferation of cells harboring the p53Y220C mutation. Altogether, AceTAC is an invaluable and powerful chemical biology platform to illuminate the human protein acetylome.

1:45 Identification of Small Molecule Pan-TEAD Inhibitors Targeting Gastric Cancer Cells

Ramesh Kumar, PhD, Principal Investigator & Scientist, Institute of Molecular and Cell Biology, Agency for Science, Technology and Research (A*STAR)

Elevated YAP/TAZ-TEAD activity has been implicated in multiple cancer types at various stages of cancer progression. We report novel small molecule Pan-TEAD inhibitors that form covalent complexes with a cysteine in the TEAD palmitoylation site. Compounds translocate YAP into the cytoplasm and inhibit TEAD transcriptional target genes in cancer cells. TEAD1 dependency of gastric cancer cell lines enhance cellular sensitivity in responses to small molecule Pan-TEAD inhibitors.

2:15 Targeting MYC with Modular Synthetic Transcriptional Repressors Derived from bHLH DNA-Binding Domains

Raymond Moellering, PhD, Associate Professor, Department of Chemistry, University of Chicago

We report a chemical strategy to generate modular synthetic transcriptional repressors (STRs) derived from the bHLH domain of MAX. Our synthetic approach yields chemically stabilized tertiary domain mimetics that cooperatively bind the MYC/MAX consensus E-box motif with nanomolar affinity, exhibit specificity that is equivalent to or beyond that of full-length TFs, and directly compete with MYC/MAX protein for DNA binding.

2:45 Sponsored Presentation *(Opportunity Available)*

3:00 Networking Refreshment Break

3:15 Developing and Applying a Novel Chemoproteomics Platform for Transcription Factor Drug Discovery

Sherry Niessen, PhD, Vice President, Proteomics, Belharra Therapeutics

Belharra Therapeutics is the next wave in chemoproteomics focused on applying a novel chemistry enabled non-covalent probe library and quantitative mass spectrometry to identify chemical probes that selectively bind any pocket, on any protein, in live cells. Most proteins identified as being selectively engaged by our probe library do not have a reported ligand, demonstrating the ability to identify novel pockets and potential chemical probe starting points for these targets.

3:45 Targeting the Hippo Pathway in Cancers

Anwesha Dey, PhD, Director & Distinguished Scientist, Discovery Oncology, Genentech Inc.

The Hippo signaling pathway is an evolutionarily conserved pathway that plays a role in development and homeostasis. The TEAD family of the transcription factors are the major transcription factors of the Hippo pathway. TEADs regulate many biological processes, including development, tissue homeostasis, and tumorigenesis by regulating cellular proliferation and survival. Identification of the underlying mechanisms to Hippo pathway inhibition would allow us to develop effective combination therapeutic strategies.

4:15 Targeting Transcription Factors with Intracellular Antibodies and Using the Antibody Paratopes for Chemical Surrogates

Terence Rabbitts, FRS, FMedSci, Professor, Molecular Immunology, Center for Cancer Drug Discovery, Institute of Cancer Research

Chromosomal translocation-proteins are hard-to-drug proteins in cancer since these often encode transcription factors. Intracellular antibodies are starting points as inhibitors blocking protein-protein interactions and can be engineered with effector functions such as E3 ligases to create biodegraders. The intracellular antibody binding site can also be used to screen for small molecule surrogates, using a new antibody-derived (Abd) technology. These approaches will be discussed, targeting the transcription factor LMO2.

5:00 Close of Symposium

5:30 Dinner Short Course Registration

6:00 Dinner Short Courses*

*Premium Pricing or separate registration required. See Short Courses page for details.

Covalent Modifications & Induced Proximity

Innovative Chemistries and Assays for Studying and Modulating Cellular Interactions

MONDAY, APRIL 1

12:00 pm Pre-Conference Symposium Registration

1:00 Welcome Remarks

1:10 Chairperson's Remarks

Daniel A. Erlanson, PhD, Senior Vice President, Innovation and Discovery, Frontier Medicines Corporation

1:15 Lessons for Covalent Drug Development from ADME and Chemoproteomic Profiling of Approved Covalent Drugs

Micah Niphakis, PhD, Director, Chemical Biology, Lundbeck La Jolla Research Center

To gain deeper insights into the behavior of covalent drugs in physiological settings, we conducted a comparative analysis of a diverse range of approved covalent drugs. Employing chemoproteomics, we investigated their target profiles, while also examining properties commonly assessed during drug development. We anticipate that these findings will serve as a valuable resource for scientists engaged in the development of safe and effective covalent drugs.

1:45 Cell-Based Discovery of Covalent Inhibitors for Undruggable Oncology Targets

Brent Martin, PhD, Vice President, Chemical Biology, Scorpion Therapeutics

Covalent inhibitors offer a differentiated approach to drug-challenging targets with less defined pockets in proximity to nucleophilic amino acids. Here I will discuss progress towards identifying druggable opportunities through chemoproteomic profiling, including a refined model of chemical reactivity and binding affinity to drive covalent occupancy. Examples will be presented of historically challenging target classes, including transcription factors.

2:15 Covalent Ligand Directed Release (CoLDR) Chemistry

Nir London, PhD, Senior Scientist, Organic Chemistry, Weizmann Institute of Science

Few electrophiles meet the criteria for successful covalent inhibitors. I will present a-substituted methacrylamides and sulfamate acetamides as new classes of electrophiles for Covalent Ligand Directed Release (CoLDR) chemistry. These electrophiles are tunable, and allow functionalization with variable leaving groups with applications to intracellular cargo delivery and novel proximity induction systems. Using ibrutinib as a model, we show how late-stage optimization with CoLDR 'warheads' improve its properties.

2:45 Presentation to be Announced

Fidabio
The Power of 1st Principle

3:00 Networking Refreshment Break

3:15 Sub-Stoichiometric Degradation Is Dispensable to Develop Highly-Potent PROTACs: A Case Study for Covalent BTK PROTAC

Jin Wang, PhD, Professor, Pharmacology & Chemical Biology, Baylor College of Medicine

We developed a covalent BTK PROTAC with sub-nM DC50. This compound only degrades wild type BTK, but not the C481S mutant, indicating that covalent bond formation is required to engage BTK. In-cell target engagement assay showed that the covalent BTK PROTAC is highly permeable with similar permeability to small molecule inhibitors. This case study demonstrates the possibility to develop highly potent single-turnover covalent PROTAC.

3:45 Interrogating the Druggable Proteome with Proximity Pharmacology

Fleur Ferguson, PhD, Assistant Professor of Chemistry and Biochemistry and Assistant Professor, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego

Induced proximity is a burgeoning area of research; however, much remains to be learnt about the mechanisms of induced proximity drugs and chemical probes. Here, I discuss chemical protoemic strategies to investigate the mechanism and effects of proximity-inducing molecules.

4:15 Discovery Proteomics for Investigating Interactomes

Andrew Zhang, PhD, Director, Chemical Biology, AstraZeneca

Understanding protein-protein interactions can identify new mechanisms for drug discovery and development, particularly for difficult targets where inhibition alone is not sufficient to carry out a therapeutic effect. In this presentation, we show a "twist" on the traditional proximity ligation methods that can be conducive to identifying new modes of actions through complexes and transient interactions.

5:00 Close of Symposium

5:30 Dinner Short Course Registration

6:00 Dinner Short Courses*

*Premium Pricing or separate registration required. See Short Courses page for details.

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Inaugural

APRIL 1, 2024 | 1:00-5:00 PM

Generative AI & Predictive Modeling

Understanding the Impact of Breakthroughs in Neural Networks & Data Analytics

MONDAY, APRIL 1

12:00 pm Pre-Conference Symposium Registration

1:00 Welcome Remarks

1:10 Chairperson's Remarks
Tudor Oprea, MD, PhD, CSO, Expert Systems, Inc.

1:15 Efficient Optimization over Chemical Space with Generative AI
Jason Rolfe, PhD, Co-Founder & CTO, Variational AI
Chemical space contains 10^{60} synthesizable, drug-like molecules. Within this enormous space, generative AI promises to find optimized molecules with fewer queries and less data. However, many popular techniques, such as Bayesian optimization and reinforcement learning, cannot efficiently navigate latent representations of chemical space. We show that gradient-based optimization is significantly more effective. Combining this with a novel, domain-specific architecture, we demonstrate efficient generative AI for drug discovery.

1:45 Generative AI with Synthesizability Guarantees Identifies Potent Antagonists for a G-Protein-Associated Melanocortin Receptor in a Tera-Scale vHTS Screen
Henry van den Bedem, PhD, Senior Vice President, Machine Learning Research & Cheminformatics, Atomwise Inc.
Commercially available virtual, synthesis-on-demand chemical catalogs are expanding rapidly with trillions of compounds and increasingly complex chemistry, providing value throughout all pre-clinical drug development stages. However, their exponential growth poses significant challenges for traditional search-and-score methods to efficiently explore catalogs. Here, we present and experimentally validate a generative AI that efficiently designs catalog compounds with desired properties.

2:15 Has Deep Generative AI Had an Impact on Small Molecule Design?
Daniel Seeliger, PhD, Associate Vice President, Head of Small Molecule Drug Design, Exscientia
In this talk we describe our use of generative AI for the design of small molecules. We talk about the importance of automation in input data generation and the power of generative models for small molecule design.

2:45 Sponsored Presentation *(Opportunity Available)*

3:00 Networking Refreshment Break

3:15 End-to-End Discovery of Antibodies with Dual Epitope and Tissue Specificity
Alexander Taguchi, PhD, Director, Machine Learning, Antibody Discovery, iBio, Inc.
Therapeutic antibody discovery is challenging due to an inability to control the epitope binding site and toxicity. These problems are overcome with ML design of peptides that match the sequence and structure of the target epitope. Antibody libraries are screened against the engineered peptides for efficient discovery of on-epitope binders. The antibodies are then masked with these peptides to improve their off-tissue safety profiles in the case of oncology targets.

3:45 Fine-Tuning Molecular Language Models to Learn the Kinase Inhibitor Chemical Space
Rayees Rahman, PhD, Co-Founder & CEO, Harmonic Discovery
Most out-of-the-box generative chemistry models struggle to encode the chemical properties that medicinal chemists favor during drug discovery campaigns. By fine-tuning molecular language models for specific chemical spaces, such as the kinase inhibitor chemical space, we can align generated molecules more closely with chemists' preferences.

4:15 One GPT to Rule Them All: Large Language Model-Based Platform for Target and Ligand Identification
Tudor Oprea, MD, PhD, CSO, Expert Systems, Inc.
Our team is developing a suite of LLM experts, each focused on different tasks and activities related to early drug discovery. These include PharosGPT (targets, diseases, ligands), litGPT (learn from papers), ChEMBLGPT (compounds and bioactivities) and ActivityGPT (predict bioactivity endpoints) provide LLM-based support for our projects. DrugInteLLM is the human-facing orchestra conductor that oversees our GPT-based platform for target and ligand discovery.

5:00 Close of Symposium

5:30 Dinner Short Course Registration

6:00 Dinner Short Course*
SC3: Fundamentals of Generative AI for Drug Discovery
*Premium Pricing or separate registration required. See Short Courses page for details.

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Degraders & Molecular Glues - Part 1

Designing and Optimizing PROTACs and Glues for Pursuing Undruggable Targets

6:00 pm MONDAY, APRIL 1: Dinner Short Course*

SC1: Protein Degraders: A Beyond Rule of Five Space and *in vitro* ADME Perspective

*Premium Pricing or separate registration required. See Short Courses page for details.

TUESDAY, APRIL 2

7:00 am Registration Open and Morning Coffee

8:00 Welcome Remarks

DEGRADER OPTIMIZATION STRATEGIES

8:05 Chairperson's Remarks
Thomas Cummins, PhD, Chemist, Chemistry, Bristol Myers Squibb

8:10 Discovery of CC-99282, a CELMoD® Agent for Relapsed or Refractory (RR) Lymphomas
Thomas Cummins, PhD, Chemist, Chemistry, Bristol Myers Squibb
The discovery of CC-99282, a CELMoD® agent, was designed to address the needs of patients with relapsed or refractory (RR) lymphomas, often face poor prognosis and limited life expectancy. The structure-activity relationship, preclinical drug metabolism and pharmacokinetics, and antitumor efficacy data leading up to the discovery and selection of the novel protein degrader CC-99282 will be shared.

8:40 *In vitro* and *in vivo* Characterization of Selective CBP and EP300 Degraders
Kevin Wilson, PhD, Vice President, Chemistry, Foghorn Therapeutics
CREB binding protein (CBP) and E1A binding protein (EP300) are paralog histone acetyltransferases that act as transcriptional co-activators. Dysregulation of one or both proteins has been implicated in various cancers, and functional genomic screens have demonstrated a bidirectional synthetic lethal relationship between these genes in tumor cells. This talk will describe our progress in optimizing heterobifunctional degraders that are highly selective for each of these highly homologous proteins.

9:10 Optimization of Binders to DCAF1 and Their Use to Develop PROTACs
Rima Al-Awar, PhD, Head, Therapeutic Innovation & Drug Discovery, Ontario Institute for Cancer Research
DCAF1 is a substrate receptor of two distinct E3 ligases (CRL4DCAF1 and EDVP) and plays an important role in protein degradation and many cellular processes. We have identified binders to DCAF1 and will describe the optimization of these compounds and their use in the degradation of a protein of interest using a PROTAC approach.

9:40 Presentation to be Announced

9:55 Sponsored Presentation *(Opportunity Available)*

10:10 Networking Coffee Break

10:35 Insights from a Decade of Research on Orally Bioavailable PROTAC Degraders at Arvinas
Keith Hornberger, PhD, Senior Director, Chemistry, Arvinas Inc.
Proteolysis targeting chimera (PROTAC) protein degraders are heterobifunctional small molecules that recruit a protein of interest to an E3 ubiquitin ligase, leading to proteasomal degradation of the target protein. This presentation will: 1) provide a brief overview of the PROTAC technology; 2) discuss physicochemical property guidelines for attaining oral absorption in the beyond-rule-of-5 space occupied by PROTAC degraders.

11:05 PANEL DISCUSSION: Preclinical Safety Considerations for Degraders and Glues
Moderator: Mary Matyskiela, PhD, Vice President, Molecular Sciences, Neomorph, Inc.
Panelists:
Suzana Couto, PhD, Senior VP, Pathology & Toxicology, Neomorph Inc.
Brandon D. Jeffy, PhD, DABT – Director, Drug Safety Research & Evaluation, Takeda San Diego
Matthias Wittwer, PhD, Project Leader, DMPK-PD, Pharmaceutical Sciences, Roche Pharma

12:05 pm Transition to Lunch

12:10 LUNCHEON PRESENTATION: Luncheon Presentation to be Announced
eurofins | DISCOVERY
Speaker to be Announced

12:40 Session Break

NEW E3 LIGASES AND LIGANDS FOR DEGRADATION

1:30 Chairperson's Remarks
Matthew Calabrese, PhD, Senior Director & Head, Structural & Molecular Sciences, Pfizer Global R&D

1:35 Exploring Suitable E3 Ligase Binders for Discovery of Targeted Protein Degraders through a Phenotypic-First Approach
Shigeru Furukubo, PhD, Principal Scientist, Chemistry, FIMECS Inc.
We have develop a proprietary platform technology, RaPPIDS (Rapid Protein Proteolysis Inducer Discovery System) with highly productive synthesis and evaluation, leading a drug candidate of IRAK-M degrader, FIM-001. The platform has been continuously improved and extended to identify novel E3 ligase binders by taking a phenotypic-first approach. This is an innovative strategy to select a suitable E3 ligase for a protein of interest and the discovery of novel PROTAC degraders.

2:05 Discovery of Novel E3 Ligands for Targeted Protein Degradation
Yue Xiong, PhD, Co-Founder & CSO, Cullgen
Targeted protein degradation by its catalytic mechanism achieves high efficacy, the ability to target previously undruggable proteins, and potential to deliver drug activity to selective tissues. All three features depend on the E3 ligands, which are currently limited despite the expression of more than 600 E3 ligases in human cells. I will discuss our rationale and efforts in the discovery, DMPK properties and use of novel E3 ligands.

2:35 Leveraging Our File to Find Novel Ligands for an E3 Ligase
Matthew Calabrese, PhD, Senior Director & Head, Structural & Molecular Sciences, Pfizer Global R&D
This talk will describe a strategy leveraging our internal file through a binding-first Hit ID approach to identify ligands for a new E3 ligase. Potency optimization was achieved using structure-based drug design (SBDD), resulting in the development of novel chemical tools to explore target biology.

3:05 Presentation to be Announced
PELAGO BIOSCIENCE

3:20 Grand Opening Refreshment Break in the Exhibit Hall with Poster Viewing and Best of Show Voting Begins

PLENARY KEYNOTE SESSION

4:20 Plenary Welcome Remarks from Lead Content Director with Poster Finalists Announced
Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

4:30 PLENARY KEYNOTE: Applications of SuFEx Click Chemistry for Drug Discovery and Chemical Biology

Barry Sharpless, PhD, Professor, Chemistry, Scripps Research Institute; 2022 and 2001 Nobel Laureate

My work has been guided by the modular simplicity of nature—the fact that all molecules of life are made from several dozen building blocks. Here I will discuss the Sulfur(VI) Fluoride Exchange (SuFEx), a second near-perfect click chemistry reaction pioneered here at Scripps. SuFEx allows reliable molecular connections to be made under metal-free conditions. I will include applications in drug discovery, chemical biology, and polymer chemistry.

5:15 Welcome Reception in the Exhibit Hall with Poster Viewing

6:15 Close of Day

WEDNESDAY, APRIL 3

7:15 am Registration Open

7:45 In-Person Breakouts with Continental Breakfast

NOVEL DEGRADATION APPROACHES & MODALITIES

8:30 Chairperson's Remarks

Pat Sharp, PhD, Co-Founder and Vice President, Discovery Sciences, Gate Bioscience

8:35 Single Amino Acid-Based PROTACs and Beyond

Hai Rao, PhD, Professor and Chair, Department of Biochemistry, Southern University of Science and Technology, China

We have developed a set of single amino acid-based PROTACs for target destruction by the N-end rule pathway. The modular design described offers unique advantages, including high potency, degradation rate modulation with different amino acids, and smaller molecular size with shortest degradation sequences. We demonstrate the utility and efficacy of these PROTACs, furthering expanding the repertoire of limited degrons and pathways available for PROTACs in the fight against various cancers.

9:05 Peptidic Macrocycles as Suitable Bioactive Scaffold for Targeted Protein Degradation

Jakob Fuhrmann, PhD, Senior Principal Scientist, Peptide Therapeutics, Genentech, Inc.

The development of proximity-induced degraders still poses several challenges, including their relatively low cell-permeability, as well as high degree of conformational flexibility due to the presence of flexible linker elements. I will present our strategy to identify conformationally constrained macrocyclic degraders. I will further highlight our characterization cascade comprising ternary complex stabilization, as well as property-based optimizations to obtain *in vivo* bioactive compounds.

9:35 Coffee Break in the Exhibit Hall with Poster Awards Announced

(Sponsorship Opportunity Available)

10:30 Molecular Gates: Discovery and Development of Substrate-Selective Small-Molecule Modulators of Sec61

Pat Sharp, PhD, Co-Founder and Vice President, Discovery Sciences, Gate Bioscience

Molecular Gates are small molecule modulators of Sec61 that block the biogenesis of specific secretory and membrane proteins. Blocking the synthesis of newly-formed proteins at translocation has potential pharmacological advantages over proximity-induced protein degradation. This presentation will discuss recently published work on cyclic peptide natural product derivatives (cotransins) that act at Sec61 and their optimization for substrate-selectivity.

11:00 Targeted Protein Degradation via Intramolecular Bivalent Glues

Ollie Hsia, PhD, Postdoctoral Research Assistant, Laboratory of Dr. Alessio Cuilli, Center for Targeted Protein Degradation, University of Dundee

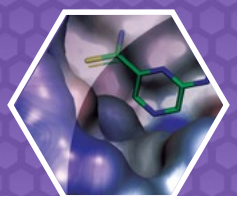
We have structurally resolved the mode of action of bifunctional BRD4 degraders and shown that—instead of connecting target and ligase in trans—they simultaneously engage two adjacent domains of the target protein in cis. This conformational change glues BRD4 to the E3 ligases DCAF11 or DCAF16, leveraging intrinsic but non-functional target-ligase affinities. We thus introduce a new modality in targeted protein degradation, termed intramolecular bivalent glues (IBGs)

11:30 Polymerization-Inducing Chimeras—A New Bifunctional Modality

Nir London, PhD, Senior Scientist, Organic Chemistry, Weizmann Institute of Science

PINCHs (Polymerization-Inducing Chimeras) are bifunctional molecules that are able to bind two separate monomers of obligatory biological multimers, and therefore can create long polymers of said complexes. We show efficient induction of intracellular polymerization and precipitation of two select targets—Keap1 and BCL6, both homodimeric proteins. We anticipate targeted induced aggregation to have a differentiated phenotypic profile and serve as an alternative modality to targeted inhibition or degradation.

12:00 pm Close of Degraders – Part 1 Conference



Fragment-Based Drug Discovery

Fragment-Based Lead Design (FBLD) for New Small Molecule Therapeutic Candidates

6:00 pm MONDAY, APRIL 1: Dinner Short Course*

SC2: Fragment-Based Drug Design: Advancing Tools and Technologies

*Premium Pricing or separate registration required. See Short Courses page for details.

TUESDAY, APRIL 2

7:00 am Registration Open and Morning Coffee

8:00 Welcome Remarks

FRAGMENT-BASED DRUG DISCOVERY (FBDD) INNOVATIONS

8:05 Chairperson's Remarks

Matthew A. Marx, PhD, Senior Vice President, Drug Discovery, Mirati Therapeutics, Inc.

8:10 Assessing Highly Diverse Fragment Libraries by ^{19}F NMR Enables Robust Identification of Chemical Starting Points for Challenging Drug Targets

Andreas Lingel, PhD, Associate Director, Global Discovery Chemistry, Novartis Institutes for Biomedical Research

Hit and lead generation by fragment-based methods has become an established approach which is now routinely applied alongside complementary methods in early drug discovery, with ^{19}F NMR-based methods proven to be of particular utility as they offer unique advantages. In this presentation, recent developments which increase the feasibility of assessing large and chemically diverse libraries by ^{19}F NMR as well as case studies of difficult-to-drug targets will be discussed.

8:40 Computational Hot-Spot Mapping for Fragment-Based Drug Discovery

Diane M. Joseph-McCarthy, PhD, Professor of the Practice, Biomedical Engineering, Boston University

Identification of fragment-binding positions on the surface of macromolecules is a key to assessing the druggability of novel targets. Computational hot-spot mapping was performed to identify binding sites across a set of known or potential drug targets, and a novel approach for clustering was employed to select top druggable sites, including allosteric sites. The utility of experimentally determined vs. AlphaFold-generated models was also assessed within this context.

9:10 Fragments to Leads: Accelerating Discovery by Rapid Screening of Giga-Scale On-Demand Chemical Spaces

Vsevolod "Seva" Katritch, PhD, Professor, Quantitative and Computational Biology and Chemistry, University of Southern California

Rapid synthon-based screening approaches like V-SYNTHES have shown practical utility in hit and lead discovery for many clinically relevant targets, however, like any structure-based method it is limited to the structurally well-defined binding pockets. Here, we explore the new approaches to incorporate experimental information obtained in classical fragment screening into the V-SYNTHES pipeline to discover potent lead-like and drug-like ligands for cryptic pockets usually considered undruggable.

9:40 Exploring protein-protein interactions by Weak Affinity Chromatography (WAC™) - An IL-23 case study

WAC™ Weak Affinity Chromatography

Björn Walse, PhD, CEO, SARomics Biostructures AB

The advantage of WAC™ for FBS are the detection of weak binders by screening fragments at low concentrations (<5 µM) and its immediate ranking of hits. Here we present the result of a WAC™ screen towards IL-23 with hit validation by NMR, TSA and X-ray crystallography.

9:55 Presentation to be Announced

ZOBIO

10:10 Networking Coffee Break

HIT-TO-LEAD STRATEGIES & SUCCESSES

10:35 FEATURED PRESENTATION: Integrating FBDD and DEL Approaches for Lead Generation

Chaohong Sun, PhD, Senior Director, Lead Discovery, AbbVie, Inc.

In this presentation, I will discuss different hit generation approaches and highlight the opportunities of integrating FBDD and DEL for challenging target classes.

11:05 Beyond Affinity: Dissecting the Kinetic Landscape of Turnover Inhibitors of Nicotinamide N-Methyl Transferase (NNMT) and *in vivo* Verification of the Inhibitory Mechanism

Tomas Akerud, Associate Principal Scientist, Global Structural Chemistry, AstraZeneca R&D

A screen of 17k fragments identified 3 classes on NNMT inhibitors. One of the classes were turnover inhibitors which are substrates of the enzyme. We characterized this inhibitory mechanism in detail using a newly developed surface biosensor methodology that quantify enzymatic turnover. Systematic medicinal chemistry resulted in identification of more potent, extremely ligand efficient, inhibitors, for which we were able to verify the inhibitory mechanism *in vivo*.

11:35 Fragment-Based Discovery of Allosteric Probes of Protein Tyrosine Phosphatases

Virgil Woods, Senior Graduate Student, Laboratory of Daniel Keedy, Biochemistry, City University of New York

Leveraging crystallographic fragment screening and machine learning, we discovered allosteric binders and inhibitors of PTP1B, a validated diabetes and cancer target that presents challenges for active site druggability. We characterized these ligands using HDX-MS, revealing diverse effects on conformational dynamics. These results, complemented with recent room-temperature fragment studies, exemplify how allosteric drug design for challenging therapeutic targets can be further improved by methods that enable monitoring of protein dynamics.

12:05 pm Transition to Lunch

12:10 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

12:40 Session Break

COVALENT FRAGMENTS

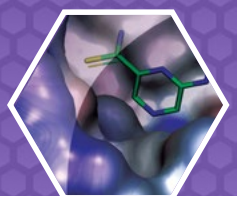
1:30 Chairperson's Remarks

Daniel A. Erlanson, PhD, Senior Vice President, Innovation and Discovery, Frontier Medicines Corporation

1:35 Ligand Efficiency Metrics in Covalent Drug Discovery

Benjamin Horning, PhD, Scientist, Vividion Therapeutics

Ligand efficiency metrics have made a major impact in medicinal chemistry, from the prioritization of early hits through lead optimization. With the ascendancy of covalent inhibitors in drug discovery, it is important to consider how to translate efficiency metrics to covalent modalities. Herein, we introduce ligand reactivity efficiency (LRE) as a means of correcting potency for intrinsic electrophilic reactivity, and explore kinetic regimes in which this analysis is appropriate.



Fragment-Based Drug Discovery

Fragment-Based Lead Design (FBLD) for New Small Molecule Therapeutic Candidates

2:05 Structure-Based Approaches Uncover Distinct Binding Modes for Covalent and Non-Covalent Ligands

Alex Berndt, PhD, Structural Biologist, Astex Pharmaceuticals Ltd

Astex has pioneered the application of structure-based approaches in drug discovery. I present a case study where crystal engineering was used to trap a therapeutic target protein kinase in distinct conformational states and deliver novel soakable crystal systems. This allowed the characterization of binding modes and mechanism-of-action of covalent and non-covalent compounds currently in the clinic. The combined results identified strategies to dial-out off-target effects and improve ligand selectivity.

2:35 Identification of Unprecedented Binding Sites by Electrophilic MiniFrags

Gyorgy Keseru, PhD, Professor, Medicinal Chemistry, Research Centre for Natural Sciences (RCNS), Hungary

We developed the covalent alternatives of Astex's MiniFrags that allow mapping potential binding sites for covalent inhibitors. Covalent MiniFrags are 5- and 6-membered electrophilic heterocycles that covalently bond at their binding site. Screening hits can be identified by simple biochemical assay, and the binding site can be located by mass spectrometry. The utility of this methodology was demonstrated by discovering the first leadlike covalent inhibitor of HDAC8.

3:05 Presentation to be Announced

Selvita

3:20 Grand Opening Refreshment Break in the Exhibit Hall with Poster Viewing and Best of Show Voting Begins

PLENARY KEYNOTE SESSION

4:20 Plenary Welcome Remarks from Lead Content Director with Poster Finalists Announced

Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

4:30 PLENARY KEYNOTE: Applications of SuFEx Click Chemistry for Drug Discovery and Chemical Biology

Barry Sharpless, PhD, Professor, Chemistry, Scripps Research Institute; 2022 and 2001 Nobel Laureate

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5:15 Welcome Reception in the Exhibit Hall with Poster Viewing

6:15 Close of Day

WEDNESDAY, APRIL 3

7:15 am Registration Open

7:45 In-Person Breakouts with Continental Breakfast

FRAGMENT-POCKET FINDING

8:30 Chairperson's Remarks

Maricel Torrent, PhD, Principal Research Scientist, Computational Drug Discovery, AbbVie, Inc.

8:35 Exploring Hidden Pockets: Using Experimentally Driven MD Simulations for Structure-Based Drug Design

Benjamin Walters, PhD, Senior Principal Scientist, Genentech, Inc.

We present a method using HDX to guide small molecules into cryptic pockets with unprecedented success rates. A cryptic pocket is a binding site that requires the ligand in order to exist, presenting a formidable challenge for computational drug discovery. The method will be described using a dynamic kinase with solved X-ray structures reflecting many binding modes before demonstrating its utility on a fragment-based drug discovery program to enabled SBDD.

9:05 Turning Cryptic Pockets into Drugs: Using (Bio)Synthetic Probes to Land in Drug-Like Chemical Space

Jerome M. Fox, PhD, CEO, Think Bioscience

I'll present how we program microbes to build small-molecule modulators that bind to cryptic pockets. We use these pockets to guide the discovery of novel hits in drug-like chemical space. Our pocket-finding probes are sp3-rich and largely nonpolar; our final hits are soluble, drug-like, and amenable to rapid chemical elaboration.

9:35 Coffee Break in the Exhibit Hall with Poster Awards Announced

(Sponsorship Opportunity Available)

FRAGMENT-BASED APPROACHES FOR IMMUNO-AND-INFLAMMATION RELATED TARGETS

10:30 FEATURED PRESENTATION: Fragment-Based Screening for SARS-CoV Drug Discovery

Stephen W. Fesik, PhD, Professor of Biochemistry, Pharmacology & Chemistry; Orrin H. Ingram II Chair in Cancer Research, Vanderbilt University

Although vaccines can prevent SARS-CoV-2 infection, variants have emerged that produce resistance. New small-molecule anti-virals that inhibit COVID-19 are needed. Papain-like protease cleaves the polypeptide of the virus and is required for viral replication. Using an NMR-based fragment screen, we identified hits that bind to the protein, optimized these hits using structure-based design, and developed potent covalent and noncovalent inhibitors of the enzyme that block viral replication.

11:00 Fragment Hit-Finding Campaigns against Ubiquitin Ligases

Charles Wartchow, PhD, Associate Director, Global Discovery Chemistry, Novartis Institutes for BioMedical Research

An important challenge for ligase-based targeted protein degradation (TPD) is identifying new ligands for existing ligases. Because ubiquitin ligases are usually part of a multi-subunit protein that contains one or more binding partners, hit-finding assays need to differentiate binding locations. To identify new chemotypes for the VHL and cereblon ligases, we used various hit finding methods including fragment screening. I will describe our results and the complexities we encountered.

11:30 Search for Selective Inhibitors of Tau-Tubulin Kinase 1 (TTBK1) Using a Fragment-Based Lead-Discovery Approach

Sriram Tyagarajan, Associate Principal Scientist, Discovery Chemistry, Merck Sharp & Dohme LLC

A fragment-based screening strategy was employed to identify allosteric binders for tau tubulin kinase 1 (TTBK1). Several hit classes identified by leveraging biophysical, computational, and crystallographic approaches were prioritized based on the biophysical profile, potential ligandability, and potential of binding site for inhibitory selectivity. The identified allosteric pockets and corresponding fragment hits will be discussed with regard to their potential and early elaboration to provide kinome selectivity for TTBK1.

12:00 pm Close of Fragment Conference

AI/Machine Learning for Early Drug Discovery - Part 1

AI-Driven Decision-Making for Drug Design, Screening, and Lead Optimization

6:00 pm MONDAY, APRIL 1: Dinner Short Course*

SC3: Fundamentals of Generative AI for Drug Discovery

*Premium Pricing or separate registration required. See Short Courses page for details.

TUESDAY, APRIL 2

7:00 am Registration Open and Morning Coffee

8:00 Welcome Remarks

AI/ML & REAL-WORLD APPLICATIONS

8:05 Chairperson's Remarks
Tudor Oprea, MD, PhD, CSO, Expert Systems, Inc.

8:10 AI in Healthcare: Where We Are and Where We Can Go
Karlie Sharma, PhD, Program Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health
The importance of using AI in healthcare is well emphasized in the clinical community but translating such innovative tools for clinical applications and physician/patient utilization remains a challenge. I will highlight several unique challenges that have impeded the progress of AI in healthcare and will discuss some potential resources that could inform the implementation of AI in clinical practice, allowing clinicians to better diagnose and treat patients.

8:40 Real-World Data Meets the Drug Development Pipeline
Michael Liebman, PhD, Managing Director, IPQ Analytics, LLC
Currently, real-world data in pharma most frequently supplements clinical trials and complements regulatory submissions, however this may miss the real opportunity to improve target selection and drug development. RWD, focused on clinical data rather than operational data—and applied in early drug discovery—can significantly improve disease (and patient) stratification and reduce failure rates. Disease is a process, leading to "next-generation phenotyping." Examples from women's health will be presented.

9:10 Combining Active Learning, Synthesis-on-Demand Libraries, and Fragment Screening in Early Drug Discovery
Patrick Walters, PhD, Chief Data Officer, Relay Therapeutics, Inc.
The advent of ultra-large screening libraries has created opportunities and challenges for virtual screening. With multi-billion molecule libraries like the Enamine REAL and WuXi GalaXi collections, brute-force evaluation is no longer a viable alternative. To meet this need, computational groups are developing active learning methods that use machine learning models as surrogates for more computationally (and economically) expensive calculations. This presentation will highlight applications of one such method, Thompson Sampling.

9:40 Presentation to be Announced

10:10 Networking Coffee Break

10:35 The Future Now: AI and Drug Discovery
Jose Duca, PhD, Global Head Computer Aided Drug Discovery, Global Discovery Chemistry, Novartis Institutes for Biomedical Research Inc.
We live in a unique and exciting time. This presentation will showcase the latest developments in modeling, generative methods, and drug discovery, using real-life examples. The talk will emphasize that success in this field requires a combination of AI deployment and molecular thinking, as well as adherence to first principles. A culture revolution is currently underway, which enables the acceleration of higher-quality results.

11:05 PANEL DISCUSSION: How Can We Best Utilize AI/ML to Maximize Impact & Efficiency?
Moderator: Tudor Oprea, MD, PhD, CSO, Expert Systems, Inc.
Panelists:
Jose Duca, PhD, Global Head Computer Aided Drug Discovery, Global Discovery Chemistry, Novartis Institutes for Biomedical Research Inc.
Michael Liebman, PhD, Managing Director, IPQ Analytics, LLC
Karlie Sharma, PhD, Program Officer, National Center for Advancing Translational Sciences (NCATS), National Institutes of Health
Patrick Walters, PhD, Chief Data Officer, Relay Therapeutics, Inc.

12:05 pm Transition to Lunch

12:10 LUNCHEON PRESENTATION: Luncheon Presentation to be Announced

Sang Eun Jee, Dr., Application Scientist, XtalPi Inc

12:40 Session Break

AI-DRIVEN DRUG DESIGN

1:30 Chairperson's Remarks
Petrina Kamya, PhD, Head of AI Platforms and President, Insilico Medicine, Canada

1:35 Leveraging AI to Design and Optimize Selective CDK20 Inhibitors
Petrina Kamya, PhD, Head of AI Platforms and President, Insilico Medicine, Canada
From identifying a dark target implicated in hepatocellular carcinoma to leveraging an AlphaFold2 predicted target for the design of tool molecules, during this talk, I will take on the next chapter in this story: optimization of our CDK20 inhibitors using AI.

2:05 Scale-Up Your Experts: Harnessing AI for Augmented Fragment-Based Drug Discovery
Marcel Verdonk, PhD, Senior Director, Computational Chemistry & Informatics, Astex Pharmaceuticals
The rich structural context of fragment-based drug discovery opens up unique opportunities for artificial intelligence (AI) to assist us with the design of preclinical candidates. Here we discuss ideas around augmented fragment-based drug discovery as a strategy that integrates AI-driven approaches with human expertise—thus adding scale to the tradition of carefully handcrafted design.

2:35 Large Language Model-Based Platform for Target and Ligand Identification
Tudor Oprea, MD, PhD, CSO, Expert Systems, Inc.
Our team has developed DrugInteLLM, a suite of LLM experts, each focused on different tasks and activities related to early drug discovery. PharosGPT (targets, diseases, ligands from pharos.nih.gov), litGPT (learn from papers), ChEMBLGPT (compounds and bioactivities) and ActivityGPT (predict bioactivity endpoints) provide LLM-based support for our projects. We will describe our platform for target and ligand selection, and how GPTs can support drug discovery.

3:05 CDD Vault and Assay Annotation Ontologies: Fueling AI/ML with Usable Data

Kelly Bachovchin, Customer Engagement Scientist, Collaborative Drug Discovery
CDD Vault's Assay Annotation streamlines drug discovery data management, aligning assay data with FAIR principles for better research confidence. The adoption of Ai/ML to aid drug discovery represents a pivotal advancement, promising to expedite drug discovery processes. This presentation will delve

AI/Machine Learning for Early Drug Discovery - Part 1

AI-Driven Decision-Making for Drug Design, Screening, and Lead Optimization

into the synergy of FAIR data principles with AI and ML technologies and how this can be further leveraged with CDD Vault's FAIR Assay Annotation Application.

3:20 Grand Opening Refreshment Break in the Exhibit Hall with Poster Viewing and Best of Show Voting Begins

PLENARY KEYNOTE SESSION

4:20 Plenary Welcome Remarks from Lead Content Director with Poster Finalists Announced

Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

4:30 PLENARY KEYNOTE: Applications of SuFEx Click Chemistry for Drug Discovery and Chemical Biology

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5:15 Welcome Reception in the Exhibit Hall with Poster Viewing

6:15 Close of Day

WEDNESDAY, APRIL 3

7:15 am Registration Open

7:45 In-Person Breakouts with Continental Breakfast

AI/ML FOR EXPLORING CHEMICAL SPACE

8:30 Chairperson's Remarks

Ghotas Evindar, PhD, Senior Vice President, Head of Drug Discovery, 1859, Inc.

8:35 Synergizing Predictive and Generative AI with Large-Scale Physical Screening for Accelerated Drug Discovery

Hossam Ashtawy, PhD, Director, Artificial Intelligence & Machine Learning, 1859 Inc.

AI/ML's potential in drug discovery is hindered by limited high-quality data. 1859 Inc.'s unique empirical platform addresses this by generating scalable, high-quality data for training generalizable predictive and generative models. Driven by this data, our novel geometric deep learning models learn bioactivity fingerprints critical for predicting protein-ligand interactions. These models have successfully identified and generated lead-like molecules, potentially reducing time and cost in lead optimization.

9:05 Effective Exploration of Giga-Large Chemical Spaces for Early Drug Discovery

Anastasiia Sadybekov, PhD, Research Scientist, Laboratory of Seva Katritch, The Bridge Institute, University of Southern California

The advent of giga-large make-on-demand combinatorial chemical spaces presents a great opportunity for drug discovery but requires novel computational approaches for fast and accurate screening. We have developed V-SYNTHES, a new iterative synthon-based approach for fast structure-based virtual screening of billions of readily available (REAL) compounds. I will discuss the latest developments of V-SYNTHES technology and its synergistic combination with machine learning tools for efficient exploration of giga-large chemical spaces.

9:35 Coffee Break in the Exhibit Hall with Poster Awards Announced

(Sponsorship Opportunity Available)

10:30 Does AI Help DEL-Based Drug Discovery?

Jeff A. Messer, Director, Analytics, Encoded Libraries Technology, GlaxoSmithKline

11:00 Machine Learning on DEL Accelerates Drug Discovery

Ching-Hsuan Tsai, PhD, Director, Relay Therapeutics, Inc.

Hit-expansion and lead-optimization constitute some of the most time-consuming and resource-intensive efforts in early small molecule drug discovery. Using a few Relay drug discovery exemplars, I will describe how Relay integrates the Dynamo Platform with DEL screening and describe how we deploy machine learning on DEL to predict hits with better drug-like properties and accelerate programs towards lead-optimization.

11:30 Construction and Selection of DELs for ML

Eray Watts, Vice President, High Throughput Chemistry, insitro

Machine learning models make better predictions of small molecule binders to proteins when they are built on better training sets. Training sets enable better models when they (i) comprise more, and diverse, true positives and negatives, and (ii) when the true positives are more accurately rank-ordered by affinity. We are building DELs and DEL selection methods that produce higher-quality training sets.

12:00 pm Close of AI/Machine Learning – Part 1 Conference

Encoded Libraries for Drug Discovery

DNA-Encoded Libraries (DELs) for Expanding Chemical Space

6:00 pm MONDAY, APRIL 1: Dinner Short Course*

SC4: DNA-Encoded Libraries

*Premium Pricing or separate registration required. See Short Courses page for details.

TUESDAY, APRIL 2

7:00 am Registration Open and Morning Coffee

8:00 Welcome Remarks

DNA-ENCODED LIBRARIES (DEL): EXPANDING CHEMICAL SPACE

8:05 Chairperson's Remarks

Rachael Jetson, PhD, Senior Director, Lead Discovery, Valo Health

8:10 FEATURED PRESENTATION: Expanding the Chemical Space of DNA-Encoded Libraries in Two and Three Dimensions

Carol Mulrooney, PhD, Investigator, Cheminformatics, GlaxoSmithKline

This talk will focus on the design, physicochemical properties, and chemical space of DNA-encoded libraries that are synthesized and screened at GSK, and our success in finding confirmed binders and clinical candidates from these DELs. Using cheminformatics methods to evaluate the diversity and property distributions of our collections of small molecule ligands, we demonstrate that our current design strategy balances efficiency and drug-like properties while covering diverse chemical space.

8:40 Dual-Display DNA-Encoded Chemical Libraries: Novel Opportunities and Future Developments

Louise Plais, PhD, Post-Doctoral Fellow, Pharmaceutical Sciences, ETH Zurich

Our group at ETH Zürich has recently produced novel dual-display DELs with diverse encoding schemes and innovative chemical designs, including fragment-like small molecules and several macrocyclic architectures. Such libraries can be mixed-and-matched together to reach a higher level of combinatorial assembly. Potent binders were successfully obtained for a large array of targets, demonstrating the yet untapped potential of dual-display DELs for ligand discovery against important therapeutic targets.

9:10 Advancement and Application of DNA-Encoded Libraries at JNJ

Pratik R. Chheda, PhD, Scientist, DNA Encoded Library DEL, Janssen Pharmaceuticals

Over the last several years, DNA-encoded library (DEL) screens have become a critical part of Johnson & Johnson's integrated hit-finding workflow. We will highlight recent advancements and applications of our internal DEL platform including several recently developed DEL-compatible chemistries that enable expansion of DEL-accessible chemical space, key DEL platform metrics, and successful hit-ID campaigns featuring DEL screens.

9:40 Presentation to be Announced

HITGEN

10:10 Networking Coffee Break

DEL CASE STUDIES

10:35 Discovery of Potent Inhibitors That Target an Active Conformation of PARP1 Using DNA-Encoded Libraries

Kelly McCarthy, PhD, Principal Scientist, Lead Discovery, Valo Health

This presentation will explore the DEL selection campaign we designed to screen our internal library collection of ~5 billion molecules to discover novel and potent PARP1 inhibitors that do not exhibit toxic DNA trapping properties. The selection and protein design allowed us to interrogate an active, functionally relevant form of PARP1; the development of biochemical assays, alongside obtaining a crystal structure, enabled the validation of the MoA of these inhibitors.

11:05 DNA Encoded Libraries for Developing SARS-CoV-2 Mpro Inhibitors

Damian W. Young, PhD, Assistant Professor, Pharmacology & Chemical Biology, Baylor College of Medicine

We used a DNA-encoded chemistry technology (DEC-Tec) to discover inhibitors of SARS-CoV-2 main protease (Mpro) as an alternative to current strategies. The development of inhibitors for the treatment of COVID-19 has mostly benefitted from X-ray structures and preexisting knowledge of inhibitors. I will discuss how our approach provides an effficient method to generate Mpro inhibitors by circumventing such limitations.

11:35 Design and Synthesis of an RNA-Biased Library

Bernard Flynn, PhD, Professor, Medicinal Chemistry, Monash University

Our group is interested in biased-library design, until recently this has been mostly been directed to specific protein classes. However, in contrast to these earlier efforts, in this program we are designing a novel RNA-biased library for fragment (affinity) and/or biochemical screening. In this presentation we will describe our diversity-oriented synthesis approach to RNA-biased chemotypes and our screening modalities.

12:05 pm Transition to Lunch

12:10 LUNCHEON PRESENTATION: Luncheon Presentation to be Announced

WuXi AppTec

Speaker to be Announced

12:40 Session Break

DEL SCREENING INNOVATIONS & NOVEL APPLICATIONS

1:30 Chairperson's Remarks

Carol Mulrooney, PhD, Investigator, Cheminformatics, GlaxoSmithKline

1:35 Phenotypic Cellular DEL Screening in 3D (Tissue Culture)

Brian M. Paegel, PhD, Professor, Pharmaceuticals Sciences, University of California, Irvine

DEL screens typically entail affinity selection to discover ligands of the protein target. Our laboratory has previously shown that solid-phase DELs can be screened directly for biochemical activity in microfluidic droplets. In this talk, we discuss polymer engineering and 3D culture principles that have enabled DEL screening on the basis of cellular activity. I will include our first cellular activity-based DEL screen for STING agonists.

2:05 Approaches for DNA-Encoded Library Screening of Transcription Factors

Chad Hewitt, PhD, Scientist I, DNA Encoded Chemical Library Screening, Nurix Therapeutics Inc

Transcription factors and other sequence specific DNA binding proteins pose unique challenges for DNA Encoded library screening, where DNA-driven binding of DEL may lead to false positive hits. Nurix has combined multiple strategies to address this challenge and identify hits against the DNA-binding domain of the EWS-FLI1 fusion oncoprotein. This approach is widely applicable to DEL screening of DNA binding proteins.

2:35 DEL for GPCRs

Casey J. Krusemark, PhD, Associate Professor, Medicinal Chemistry & Molecular Pharmacology, Purdue University

We present novel approaches for the selection of molecules from DNA-encoded libraries using enzymatic tags on target proteins. We apply these assays for DEL discovery with GPCRs in live cells for both the discovery of ligands and for specific discovery of biased agonists.

3:05 Sponsored Presentation *(Opportunity Available)*

3:20 Grand Opening Refreshment Break in the Exhibit Hall with Poster Viewing and Best of Show Voting Begins

PLENARY KEYNOTE SESSION

4:20 Plenary Welcome Remarks from Lead Content Director with Poster Finalists Announced

Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

4:30 PLENARY KEYNOTE: Applications of SuFEx Click Chemistry for Drug Discovery and Chemical Biology

Barry Sharpless, PhD, Professor, Chemistry, Scripps Research Institute; 2022 and 2001 Nobel Laureate

My work has been guided by the modular simplicity of nature—

Encoded Libraries for Drug Discovery

DNA-Encoded Libraries (DELs) for Expanding Chemical Space

the fact that all molecules of life are made from several dozen building blocks. Here I will discuss the Sulfur(VI) Fluoride Exchange (SuFEx), a second near-perfect click chemistry reaction pioneered here at Scripps. SuFEx allows reliable molecular connections to be made under metal-free conditions. I will include applications in drug discovery, chemical biology, and polymer chemistry.

5:15 Welcome Reception in the Exhibit Hall with Poster Viewing

6:15 Close of Day

WEDNESDAY, APRIL 3

7:15 am Registration Open

7:45 In-Person Breakouts with Continental Breakfast

DEALING WITH DEL DATA: HITS TO LEADS

8:30 Chairperson's Remarks

Christopher B. Phelps, PhD, Vice President and Head, Early Discovery, Nurix Therapeutics, Inc.

8:35 A Novel Method for Normalizing Data from DNA-Encoded Library Selections

Zsofia Lengyel-Zhand, PhD, Pfizer Inc.

Strategies for DEL screening and data analysis have greatly improved, however data normalization remains an open challenge. Existing normalization methods can yield poor correlation for compounds with high copy-count and they do not account for inherent sources of noise. To overcome these drawbacks, we have developed a robust normalization technique that allows for normalization between samples of different conditions and accounts for technical challenges that occur during screening.

9:05 Bead-Encoded Libraries and ML Models to Identify and Accelerate the Advancement of Novel Kinase Inhibitors

Kenneth E. Lind, PhD, Senior Director, Informatics & Computational Chemistry, 1859 Inc.

We describe case studies demonstrating the power of our platform and the AIML models created from these data to advance molecules from hit identification through lead optimization. This includes rapid cycles of chemistry, testing *in vitro* and *in vivo* activity, and refining AIML models based on results to produce target-specific, cellularly active leads with optimized physicochemical properties.

9:35 Coffee Break in the Exhibit Hall with Poster Awards Announced

(Sponsorship Opportunity Available)

10:30 Does AI Help DEL-Based Drug Discovery?

Jeff A. Messer, Director, Analytics, Encoded Libraries Technology, GlaxoSmithKline

11:00 Machine Learning on DEL Accelerates Drug Discovery

Ching-Hsuan Tsai, PhD, Director, Relay Therapeutics, Inc.

Hit-expansion and lead-optimization constitute some of the most time-consuming and resource-intensive efforts in early small molecule drug discovery. Using a few Relay drug discovery exemplars, I will describe how Relay integrates the Dynamo Platform with DEL screening and describe how we deploy machine learning on DEL to predict hits with better drug-like properties and accelerate programs towards lead-optimization.

11:30 Construction and Selection of DELs for ML

Eray Watts, Vice President, High Throughput Chemistry, insitro

Machine learning models make better predictions of small molecule binders to proteins when they are built on better training sets. Training sets enable better models when they (i) comprise more, and diverse, true positives and negatives, and (ii) when the true positives are more accurately rank-ordered by affinity. We are building DELs and DEL selection methods that produce higher-quality training sets.

12:00 pm Close of Encoded Libraries Conference

The Medicinal Chemistry-Pharmacology Interface

The 3 Independent SARs for New Drug Candidates

TUESDAY, APRIL 2, 2024 8:00 AM - 3:20 PM | WEDNESDAY, APRIL 3, 2024 8:30 AM - 12:00 PM

Training seminar takes place in-person only

Instructor:

Terrence P. Kenakin, PhD, Professor, Pharmacology, University of North Carolina at Chapel Hill

This training seminar will cover the three independent structure-activity-relationships (SARs) that must be satisfied for new drug success: (1) Primary Target Activity, (2) Pharmacokinetic Profile, and (3) Safety.

Seminar Outline:

Day 1 (AM): SAR 1: Primary Target Activity

- (a) Affinity: What concentrations are needed in the receptor compartment for target binding?
- (b) Efficacy: How do drugs produce cellular response (drugs have many efficacies)? How the combination of signaling effects yields a 'quality' of efficacy to cells.

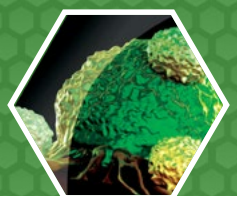
Day 1 (PM): SAR 1: Primary Target Activity (cont.)

- Efficacy/how biased-signaling causes complex patterns of efficacy (and how can this be manipulated?)
- Allosteric vs. orthosteric interaction of molecules: how allosteric interaction fundamentally differs from orthosteric (same site) interaction
- Kinetics of ligand interaction for *in vivo* target coverage: the importance of *in vivo*-restricted diffusion/importance of receptor offset rates for target coverage (PK-PD dissociation)/methods to measure kinetics

Day 2 (AM): SAR 2-Pharmacokinetic Profile and SAR 3—Safety

- SAR 2 (ADME): Methods for modification of candidate ADME properties (modification of 'druglike' activity/specific modification of interactions with recognition processes (i.e., hepatic enzymes, transporters)
- SAR 3: Safety: Basic safety issues faced early on (cytotoxicity, hepatotoxicity, hERG, Ames test)/translation of *in vitro* to *in vivo* activity

Beginning his career as a synthetic chemist, Terry Kenakin received a PhD in Pharmacology at the University of Alberta in Canada. After a postdoctoral fellowship at University College London, UK, he joined Burroughs-Wellcome as an associate scientist for 7 years. From there, he continued working in drug discovery for 25 years first at Glaxo, Inc., then Glaxo Wellcome, and finally as a Director at GlaxoSmithKline Research and Development laboratories at Research Triangle Park, North Carolina, USA. Dr. Kenakin is now a professor in the Department of Pharmacology, University of North Carolina School of Medicine, Chapel Hill. Currently he is engaged in studies aimed at the optimal design of drug activity assays systems, the discovery and testing of allosteric molecules for therapeutic application, and the quantitative modeling of drug effects. In addition, he is Director of the Pharmacology graduate courses at the UNC School of Medicine. He is a member of numerous editorial boards, as well as Editor-in-Chief of the "Journal of Receptors and Signal Transduction." He has authored numerous articles and has written 10 books on pharmacology.



Small Molecule Immuno-Modulators

Towards Anti-Cancer and Autoimmunity Therapies with Oral-Bioavailability Potential

TUESDAY, APRIL 2

7:00 am Registration Open and Morning Coffee

8:00 Welcome Remarks

IMMUNO-ONCOLOGY SMALL MOLECULE TARGETS

8:05 Chairperson's Remarks
Dean G. Brown, PhD, Vice President & Head, Chemistry, Jnana Therapeutics

8:10 HPK1 Citron Homology Domain Regulates Phosphorylation of SLP76 and Modulates Kinase Domain Interaction Dynamics
Laetitia D. Comps-Agrar, PhD, Senior Principal Scientist, Biochemical & Cellular Pharmacology, Genentech, Inc.
HPK1, a negative regulator of TCR signaling, is an attractive target for cancer immunotherapy. Although the role of HPK1 kinase domain (KD) has been elucidated, the function of its citron homology domain (CHD) remains elusive. Through a combination of structural, biochemical, and mechanistic studies, we characterized the structure-function of CHD in relationship to KD and demonstrated a central role for CHD in the regulation of HPK1 function.

8:40 The Discovery of Pyrazolopyrimidines as HPK1 Inhibitors
Daniel J Poon, PhD, Senior Director, Medicinal Chemistry, RAPT Therapeutics
Hematopoietic progenitor kinase 1 (HPK1) is a negative regulator of T cell signaling. Upon T cell receptor (TCR) stimulation, activated HPK1 phosphorylates the adaptor protein SLP76, triggering its degradation and downregulating T cell functions needed for effective anti-tumor immune responses. We present our efforts on the development of pyrazolopyrimidines as potent and selective inhibitors of HPK1 along with descriptions of their pharmacological profiles in *in vivo* PD and efficacy models.

9:10 NX-1607, a First-in-Class Inhibitor of Casitas B-Lineage Lymphoma-b (CBL-B) for Immuno-Oncology
Frederick Cohen, PhD, Vice President, Medicinal Chemistry, Nurix Therapeutics, Inc.
The E3 ubiquitin ligase CBL-B is expressed in multiple immune cell lineages and is a master regulator of immune response. NX-1607 is a molecule that glues CBL-B into an inactive conformation lowering the threshold for T cell activation. In cancer models, NX-1607 inhibits tumor growth when dosed orally. We present preclinical data on NX-1607, supporting its advancement to clinical testing, and pharmacokinetic-pharmacodynamic (PK-PD) data from the FIH trial (NCT05107674).

9:40 Sponsored Presentation *(Opportunity Available)*

10:10 Networking Coffee Break

INFLAMMATORY MEDIATORS

10:35 Discovery of A1480LS, a Covalent, Peripherally Distributing Dual Inhibitor of Serine Hydrolases DAGLα and DAGLβ for the Treatment of Chronic Pain through Suppression of Inflammatory Mediators
Jake Wiener, PhD, Senior Director of Chemistry and Deputy Site Head, Lundbeck La Jolla Research Center, Inc.
Diacylglycerol lipase (DAGL) a and ß convert diacylglycerols into monoacylglycerols including the endocannabinoid 2-arachidonoylglycerol (2-AG). Arachidonic acid (AA) derived from 2-AG can be further metabolized into proalgesic and proinflammatory eicosanoids. Inhibition of DAGLs has been explored as a mechanism distinct from NSAIDs to reduce eicosanoid production. Leveraging chemoproteomic methods, a lead optimization medicinal chemistry campaign identified A1480LS as a covalent small molecule inhibitor of DAGLa/ß that reduces pain-behavior in animals.

11:05 Betting on BET: The First Selective Brd4 BD2 Inhibitor for Inflammatory/Autoimmune Disease
Georg Duenstl, PhD, Vice President, Drug Discovery, DeepCure
We designed the first Brd4-BD2-selective inhibitor, which we are developing for inflammatory diseases. BET was an oncology therapeutic target until efficacy and tox concerns became evident. Pan-BD2 BET inhibitors have shown *in vivo* anti-inflammatory activity in multiple preclinical models, but similar concerns over thrombocytopenia have stifled development of non-selective BET inhibitors. By sharing our selective BETi program success, we hope to motivate others to pursue epigenetic regulators outside of oncology.

11:35 Targeting Chromatin Networks in Cancer
Laura J Hsieh, PhD, CEO & Founder, TippingPoint Biosciences
TippingPoint's novel platform targets the entire network of defective interactions in the cancer genome state rather than a single factor. Our approach increases specificity, reducing toxicity, and is robust against single-factor mutagenesis, reducing drug resistance. TippingPoint's platform will provide new therapies to treat cancers with poor prognosis and limited treatment options, such as glioblastomas and lung cancers.

12:05 pm Transition to Lunch

12:10 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

12:40 Session Break

TARGETING THE TUMOR MICRO-ENVIRONMENT WITH SMALL MOLECULES

1:30 Chairperson's Remarks
Brandon Rosen, PhD, Senior Scientist, Medicinal Chemistry, Arcus Biosciences

1:35 A Highly Differentiated Small-Molecule Immune Checkpoint Inhibitor Dually Targeting PD-L1 and A2AR for Cancer Therapy
Murali Ramachandra, PhD, CEO, Aurigene Discovery Technologies, Ltd.
Adenosine receptor signaling contributes to acquired resistance to PD-1/PD-L1 blockade. Studies have shown that the concurrent administration of PD-1/PD-L1 checkpoint inhibitors along with A2AR antagonists is more effective than single-agent treatments for anti-tumor efficacy. We have discovered small molecule inhibitors that dually target PD-L1 and A2AR. These inhibitors exhibit desirable drug-like properties and demonstrate significant tumor growth inhibition in syngeneic tumor models that correlates with potent immune activation.

2:05 HIF-2a Inhibitors: Discovery and Optimization
Artur Mailyan, PhD, Principal Investigator, Chemistry, Arcus Biosciences
The transcription factor hypoxia-inducible factor 2a (HIF-2a) is a key oncogenic driver in clear cell renal cell carcinoma (ccRCC). Hypoxic or pseudohypoxic conditions promote HIF-2a stabilization and transcription of pro-tumorigenic genes. Inhibition of HIF-2a has significant potential to mitigate tumor growth, particularly in cancers with a high prevalence of molecular alterations associated with pseudohypoxia. Herein, we describe the discovery and optimization of a potent series of small molecule HIF-2a inhibitors.

2:35 A Potential First-in-Class Selective ADAR1 p150 Inhibitor Suppresses Tumor Growth and Induces Anti-Tumor Immunity
Aditya Kulkarni, PhD, Founder & CSO, Avammune Therapeutics, Inc.
This is the first disclosure of a small molecule inhibitor of ADAR1. We report that ADAR1 (adenosine deaminase RNA), an RNA editing enzyme, has promising anti-tumor efficacy as monotherapy and in combination with other modalities. Herein, we outline the discovery of a potential first-in-class ADAR1 p150 inhibitor for cancer immunotherapy.

3:05 Sponsored Presentation *(Opportunity Available)*

3:20 Grand Opening Refreshment Break in the Exhibit Hall with Poster Viewing and Best of Show Voting Begins

PLENARY KEYNOTE SESSION

4:20 Plenary Welcome Remarks from Lead Content Director with Poster Finalists Announced
Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

4:30 PLENARY KEYNOTE: Applications of SuFEx Click Chemistry for Drug Discovery and Chemical Biology
Barry Sharpless, PhD, Professor, Chemistry, Scripps Research Institute; 2022 and 2001 Nobel Laureate
My work has been guided by the modular simplicity of nature—the fact that all molecules of life are made from several dozen building blocks. Here I will discuss the Sulfur(VI) Fluoride Exchange (SuFEx), a second near-perfect click chemistry reaction pioneered here at Scripps. SuFEx allows reliable molecular connections to be made under metal-free conditions. I will include applications in drug discovery, chemical biology, and polymer chemistry.

5:15 Welcome Reception in the Exhibit Hall with Poster Viewing

6:15 Close of Day

WEDNESDAY, APRIL 3

7:15 am Registration Open

7:45 In-Person Breakouts with Continental Breakfast

INNATE IMMUNE SYSTEM AND RIP KINASES

8:30 Chairperson's Remarks
Mihir Mandal, PhD, Principal Scientist, Medicinal Chemistry, Merck

8:35 FEATURED PRESENTATION: RIPK1 Inhibitors and Inflammation
Domagoj Vucic, PhD, Staff Scientist, Early Discovery Biology, Genentech
I will discuss the role of RIP1 in inflammatory bowel disease as well its role in tissue damage for other related diseases. Progress on RIP1K inhibitors will also be included.

9:05 Development of First-in-Class RIPK1 PROTACs to Overcome Resistance in Cancer Immunotherapies
Jin Wang, PhD, Professor, Pharmacology & Chemical Biology, Baylor College of Medicine
We developed a potent and specific RIPK1 degrader, LD4172, that synergizes with anti-PD1 to trigger immunogenic cell death and significantly inhibit tumor growth in immunotherapy-resistant syngeneic mouse models. The synergistic effect of LD4172 and anti-PD1 can be reversed by blocking either CD19, BAFFR, CD8, or CD40L, demonstrating that both B and T cells and their crosstalk play important roles in the antitumor immunity.

9:35 Coffee Break in the Exhibit Hall with Poster Awards Announced
(Sponsorship Opportunity Available)

FRAGMENT-BASED APPROACHES FOR IMMUNO-AND-INFLAMMATION RELATED TARGETS

10:30 FEATURED PRESENTATION: Fragment-Based Screening for SARS-CoV Drug Discovery
Stephen W. Fesik, PhD, Professor of Biochemistry, Pharmacology & Chemistry; Orrin H. Ingram II Chair in Cancer Research, Vanderbilt University
Although vaccines can prevent SARS-CoV-2 infection, variants have emerged that produce resistance. New small-molecule anti-virals that inhibit COVID-19 are needed. Papain-like protease cleaves the polypeptide of the virus and is required for viral replication. Using an NMR-based fragment screen, we identified hits that bind to the protein, optimized these hits using structure-based design, and developed potent covalent and noncovalent inhibitors of the enzyme that block viral replication.

11:00 Fragment Hit-Finding Campaigns against Ubiquitin Ligases
Charles Wartchow, PhD, Associate Director, Global Discovery Chemistry, Novartis Institutes for BioMedical Research
An important challenge for ligase-based targeted protein degradation (TPD) is identifying new ligands for existing ligases. Because ubiquitin ligases are usually part of a multi-subunit protein that contains one or more binding partners, hit-finding assays need to differentiate binding locations. To identify new chemotypes for the VHL and cereblon ligases, we used various hit finding methods including fragment screening. I will describe our results and the complexities we encountered.

11:30 Search for Selective Inhibitors of Tau-Tubulin Kinase 1 (TTBK1) Using a Fragment-Based Lead-Discovery Approach
Sriram Tyagarajan, Associate Principal Scientist, Discovery Chemistry, Merck Sharp & Dohme LLC
A fragment-based screening strategy was employed to identify allosteric binders for tau tubulin kinase 1 (TTBK1). Several hit classes identified by leveraging biophysical, computational, and crystallographic approaches were prioritized based on the biophysical profile, potential ligandability, and potential of binding site for inhibitory selectivity. The identified allosteric pockets and corresponding fragment hits will be discussed with regard to their potential and early elaboration to provide kinome selectivity for TTBK1.

12:00 pm Close of Small Molecule Immuno-Modulators Conference

Degraders & Molecular Glues - Part 2

Assay Development for New Ligases/Modulators and Induced Proximity Screening

WEDNESDAY, APRIL 3

12:00 pm Registration Open

1:30 Welcome Remarks

DEVELOPING TUMOR-SELECTIVE DEGRADERS & GLUES

1:35 Chairperson's Remarks
Rima Al-Awar, PhD, Head, Therapeutic Innovation & Drug Discovery, Ontario Institute for Cancer Research

1:40 Novel Selective Small-Molecule Degraders of SMARCA2 for the Treatment of Cancer
Simon Bailey, PhD, MBA, Executive Vice President & Head of Drug Discovery, Plexium, Inc.
Plexium has developed a novel approach to the identification of monovalent drug-like degraders of therapeutically important proteins, aided by a proprietary cellular high-throughput screening platform. In this talk, we will describe the discovery of degraders of SMARCA2 and the optimization of potency, selectivity, and PK properties of these monovalent degraders. The mechanistic basis for degradation by a novel E3 ligase will also be discussed.

2:10 Pushing the Boundary of the PROTAC Technology
Shaomeng Wang, PhD, Warner-Lambert/Parke-Davis Professor of Medicine, Pharmacology & Medicinal Chemistry; Co-Director, Molecular Therapeutics Program, University of Michigan
Our laboratory has been carrying out research in pushing the boundary in three different areas using the PROTAC technology: (1) targeting traditionally undruggable proteins; (2) developing highly selective degraders to overcome toxicity issues; (3) developing orally-bioavailable degraders to overcome drug-resistance of traditional drugs. I will present our latest progress in these three areas.

2:40 Presentation to be Announced

3:10 Refreshment & Dessert Break in the Exhibit Hall with Poster Viewing

4:00 Discovery of Molecular Glue Degraders for Intracellular Proteins and Development of Cancer-Selective Degraders for Extracellular Proteins
Weiping Tang, PhD, Professor, Pharmaceutical Sciences and Director, Medicinal Chemistry Center, University of Wisconsin-Madison
I will present our recent progress in the discovery of molecular glue degraders for intracellular proteins; it involves the sequence of rapid synthesis, phenotypic screening, proteomic profiling, and validation of hits and targets. I will also present our progress on the development of cancer-selective degraders for extracellular proteins involving novel antibody conjugates.

4:30 Computer-Aided and Structure-Guided Rational Design of Dual BCL-XL and BCL-2 PROTACs
Daohong Zhou, MD, Professor, Department of Biochemistry and Structural Biology, University of Texas Health San Antonio
PROTACs have emerged as an innovative drug development platform. However, most PROTACs have been generated empirically. Through computational modelling and mutagenesis studies, we found that lysine accessibility for ubiquitination plays an important role in determining the degradability of BCL-XL and BCL-2 by DT2216, a VHL-recruiting BCL-XL-specific PROTAC. Accordingly, we rationally designed and generated a BCL-XL and BCL-2 dual degrader, 753b, that exhibits increased anti-leukemic activity compared to DT2216.

5:00 In-Person Breakouts

5:45 Close of Day

5:45 Dinner Short Course Registration

6:15 Dinner Short Course*
SC5: Protein Degraders: An *in vivo* ADME and Safety Perspective
*Premium Pricing or separate registration required. See Short Courses page for details.

THURSDAY, APRIL 4

7:15 am Registration Open

7:45 Diversity in Chemistry Breakfast Discussion *(Sponsorship Opportunity Available)*
Grab a plate and then a seat to join one of the discussions below on growing the enterprise of chemistry (in terms of people diversity, not molecules). This session originated 4 years ago with a focus on 'Women in Chemistry', but every year the discussions raised more issues than time allowed. We're broadening the topics but breaking them into smaller discussion-focused groups; topics will include (with more details coming in February):
Paternity and Extended Leave Moderator(s): Thomas Garner, Genentech
Advancing Women in Chemistry Moderator(s): Katerina Leftheris, Vilya
Diversity, Equity, and Inclusion Efforts at Institutions & Companies Moderator(s): Michelle Arkin, UCSF

PLENARY KEYNOTE SESSION

8:30 Plenary Welcome Remarks from Lead Content Director with Poster Finalists Announced
Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

8:35 PLENARY KEYNOTE: Reimagining Druggability Using Chemoproteomic Platforms
Daniel Nomura, PhD, Professor of Chemical Biology and Molecular Therapeutics, Department of Chemistry, University of California, Berkeley
One of the greatest challenges that we face in discovering new disease therapies is that most proteins are considered "undruggable," in that most proteins do not possess known binding pockets or "ligandable hotspots" that small molecules can bind to modulate protein function. Our research group addresses this challenge by applying chemoproteomic platforms to discover and pharmacologically target unique and novel ligandable hotspots for disease therapy.

9:20 Coffee Break in the Exhibit Hall with Poster Viewing and Best of Show Awards Announced

IDENTIFYING NOVEL MOLECULAR GLUES

10:10 Chairperson's Remarks
Charly Chahwan, PhD, Co-Founder & CSO, SyntheX, Inc.

10:15 Multimodal Screening Platform for Novel Cereblon Neo-Substrates
Gisele Nishiguchi, PhD, Group Leader, St. Jude Children's Research Hospital
While the PROTAC approach to targeted protein degradation greatly benefits from rational design, the discovery of molecular glue degraders currently relies mostly on screening strategies. This paper will discuss the design of a cereblon-focused molecular glue library, and its screening in multiple assay modalities, including high-throughput proteomics. Discovery and characterization of monofunctional degraders of non-canonical cereblon neosubstrates will also be disclosed.

Degraders & Molecular Glues - Part 2

Assay Development for New Ligases/Modulators and Induced Proximity Screening

10:45 Engineering Cells to Discover Functional Protein Interaction Modulators

Maria Soloveychik, PhD, Co-Founder & CEO, SyntheX

SyntheX builds platforms to modulate protein interactions. ToRPPIDO discovers compounds that can disrupt a specific protein-protein interaction. ToRNeDO does the inverse and discovers molecular glues that bring a pre-specified E3 ubiquitin ligase and a neosubstrate of interest together to achieve targeted protein degradation. Using genetically engineered circuits, the platforms rely on intracellular drug selection—bypassing many of the bottlenecks that exist with canonical *in vitro* or computational screening approaches.

11:15 Presentation to be Announced

11:30 Rational Screening for Cooperativity in Small Molecule Inducers of Protein-Protein Associations

*Shuang Liu, PhD, Senior Scientist, Institute of Molecular & Cell Biology, A*STAR; former Postdoctoral Associate, Lab of Dr. Stuart Schreiber, Broad Institute of MIT and Harvard*

We identified a range of cooperative, noncooperative, and uncooperative compounds in a single DNA-encoded library screen with bromodomain-containing protein (BRD)9 and the VHL–elongin C–elongin B (VCB) complex. Our most cooperative hit compound, 13-7, exhibits micromolar binding affinity to BRD9 but nanomolar affinity for the ternary complex with BRD9 and VCB, with cooperativity comparable to classical molecular glues.

12:00 pm Parkin Ubiquitin Ligase Molecular Glues for Parkinson's Disease and Beyond

Tauseef Butt, PhD, President & CEO, Progenra, Inc.

Parkin ligase plays a critical role in mitophagy and mitobiogenesis. Mutations in parkin ligase lead to early onset of Parkinson's disease. The dysfunction of parkin ligase is also attributed to late onset of PD. Progenra has discovered molecular glues that bind to parkin, activate parkin function *in vitro*, and restore mitochondrial damage by inducing mitophagy in neuronal cells. Role of parkin in PD, muscle function, and dementia will be described.

12:30 Transition to Lunch

12:35 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

1:05 Refreshment Break in the Exhibit Hall with Poster Awards Announced *(Sponsorship Opportunity Available)*

MECHANISTIC & STRUCTURAL CHARACTERIZATION APPROACHES

1:55 Chairperson's Remarks

Behnam Nabet, PhD, Assistant Professor, Human Biology Division, Fred Hutchinson Cancer Center

2:00 Targeted Destruction of Oncogenic Drivers

Behnam Nabet, PhD, Assistant Professor, Human Biology Division, Fred Hutchinson Cancer Center

Targeted protein degradation technologies including the degradation tag (dTAG) system are powerful approaches to rapidly control protein abundance. This talk will describe our recent advances with the dTAG technology platform and our development of small molecule degraders with applications in refractory cancers.

2:30 Chemical Probe and Degrader Development for the Nucleosome Remodeling Factor, NURF, an Emerging Therapeutic Target

William Pomerantz, PhD, Associate Professor, Department of Medicinal Chemistry, University of Minnesota, Twin Cities

BPTF is an essential member of the nucleosome remodeling factor, NURF, and has increasingly become identified as a pro-tumorigenic factor, prompting investigations into cancer-associated mechanisms involving BPTF, including MYC and MYCN regulation. Our lab has developed the first inhibitors of the BPTF bromodomain and PHD. Building on these results I will present our efforts at developing the first BPTF degraders to study the role of this protein in pediatric cancers.

3:00 PLENARY PANEL DISCUSSION: Innovative Drug Discovery: Insights from Venture Capitalists

Co-Moderators:
Michelle Arkin, PhD, Chair and Distinguished Professor, Pharmaceutical Chemistry & Director, Small Molecule Discovery Center, University of California, San Francisco
Daniel A. Erlanson, PhD, Senior Vice President, Innovation and Discovery, Frontier Medicines Corporation

The high-risk but 'high impact-when-successful' strategy of VC investors gives them a uniquely critical lens through which to view innovation. Join us for an interactive discussion with VCs who will share the trends they are watching in drug discovery. The panel represents a variety of small and large venture firms, who provide early rounds of funding, as well as, those who invest at later or all stages.

Panelists:
Wendy B. Young, PhD, BioPharma Discovery
Rebecca Silberman, PhD, Senior Venture Associate, RA Capital Management LLC
Shyam Masrani, Principal, Medicxi
Jamie Kasuboski, PhD, Vice President, OMX Ventures
Olga Danilchanka, PhD, Principal, MRL Ventures Fund

3:45 Networking Refreshment Break

4:00 Mechanistic Profiling for Protein Degraders

Hua Xu, PhD, Director, Mechanistic Biology & Profiling, AstraZeneca

Targeted protein degradation is an emerging modality that is increasingly used to tackle challenging drug targets. In this talk, I will present the technologies we have developed and their impacts on mechanistic understanding and profiling of protein degraders. I will also share a unique protein degradation mechanism that we recently discovered for degraders of an epigenetic target.

4:30 CoraFluor-Enabled TR-FRET Assay Strategies for Facile PROTAC Profiling

Ralph Mazitschek, PhD, Assistant Professor, Harvard Medical School; Co-Director of the Chemical Biology Platform, Center for Systems Biology, Massachusetts General Hospital

We have developed novel TR-FRET-based high-throughput assay approaches based on our CoraFluor TR-FRET technology to facilitate the characterization of PROTACs and molecular glue degraders, including (a) the facile measurements of endogenous protein levels, (b) the kinetic and thermodynamic measurement of ligand binding affinities with endogenous and recombinant proteins, and (c) the quantitative determination of ternary complex cooperativity.

5:00 Anti-Viral PROTACs Incorporating Solid Phase Synthesis Technologies

Philip Thompson, PhD, Professor, Department of Medicinal Chemistry, Monash University

The diverse possibilities associated with PROTAC design and discovery supports strategic approaches built around synthetic novelty and efficiency. We are pursuing solid phase methods as a means to efficiently cover degrader chemical space, and applying it to the opportunities in anti-viral PROTAC discovery.

5:30 Close of Conference

Protein-Protein Interactions

Small Molecule Lead Discovery and Optimization for Difficult Drug Targets

WEDNESDAY, APRIL 3

12:00 pm Registration Open

1:30 Welcome Remarks

NON-DEGRADER GLUES, (DE)-STABILIZERS, AND TARGETING RAS

1:35 Chairpersonʼs Remarks

Adrian L. Gill, PhD, Senior Vice President, Medicinal Chemistry, Revolution Medicines

1:40 Multi-Ras Inhibitors

Anne Edwards, PhD, Scientist II, Revolution Medicines

RAS oncogenes are among the most frequently mutated genes in cancer, with common driver mutations occurring at codons 12, 13, and 61. Here, we describe RMC-7977, a potent, oral, non-covalent, tri-complex RASMULTI(ON) small molecule inhibitor with broad spectrum activity for the active state of both mutant and wild-type (WT) KRAS, NRAS, and HRAS variants (a RASMULTI(ON) inhibitor).

2:10 Discovery of MRTX1719: A Synthetic Lethal Inhibitor of the PRMT5/MTA Complex for the Treatment of MTAP-Deleted Cancers

Chris Smith, PhD, Executive Director, Drug Discovery, Mirati Therapeutics

The methylthioadenosine phosphorylase (*MTAP*)-encoding gene is co-deleted with p16/CDKN2a in ~10-15% of all human cancers, leading to elevated levels of the MTAP substrate methylthioadenosine (MTA) in these cancers. MTA binds Protein Arginine N-Methyl Transferase (PRMT5) to form the PRMT5/MTA complex. We describe biophysics-aided discovery of a 4-(aminomethyl)phthalazin-1(2H)-one fragment and its evolution into MRTX1719, a clinical-stage, selective inhibitor of the PRMT5/MTA complex as a potential precision medicine for treating MTAP-deleted tumors.

2:40 A Live Cell PRMT5 NanoBRET™ Target Engagement Assay to Quantify Competitive and Uncompetitive Modes of Inhibition

Promega

James Vasta, PhD, Senior Research Scientist, Research & Development, Promega Corporation

PRMT5 is an essential arginine methyltransferase that uses SAM as the methyl donor. Here we describe a novel NanoBRET™ Target Engagement assay that enables characterization of PRMT5 inhibitors with diverse inhibitory mechanisms in living cells. Both substrate- and SAM-competitive engagement are quantifiable. Moreover, MTA-uncompetitive engagement can also be quantified, facilitating the development of inhibitors that exploit the accumulation of MTA in various cancers by binding cooperatively to the PRMT5/MTA complex.

3:10 Refreshment & Dessert Break in the Exhibit Hall with Poster Viewing

4:00 Measuring Stable Interactions by SPR: Addressing the Long Residence-Time Challenge

Thomas P. Garner, PhD, Principal Scientist, Biophysics, Genentech, Inc.

Many biomolecular interactions form very long-lived complexes. These can be extremely challenging to measure leading to unfavorably long incubation times in biochemical/biophysical assays and inaccurate measurements. SPR has the advantage of measuring kinetics with high accuracy, the “chaser” method extends the range of measurable half-lives with high accuracy but are low throughput. We present adjustments to the chaser assay to improve throughput and its application to measuring protein interactions.

4:30 Targeted Degradation by Protein Destabilizing Compounds

Maurizio Pellecchia, PhD, Professor, Biomedical Sciences Division, University of California, Riverside

Targeted protein degradation is based on bifunctional ligands to recruit the ubiquitin-proteasome system. As an alternative strategy, we explored here the idea to design protein degraders based on the section of ligands that cause protein destabilization, and that in turn induce target degradation in cell. In an application of this approach, we found that agents can act as molecular crowbars that, destabilizing critical intramolecular interactions, cause protein degradation in cell.

5:00 In-Person Breakouts

5:45 Close of Day

5:45 Dinner Short Course Registration

6:15 Dinner Short Course*

SC6: Principles of Drug Design: Ligand-Receptor Interactions and More

*Premium Pricing or separate registration required. See Short Courses page for details.

THURSDAY, APRIL 4

7:15 am Registration Open

7:45 Diversity in Chemistry Breakfast Discussion *(Sponsorship Opportunity Available)*

Grab a plate and then a seat to join one of the discussions below on growing the enterprise of chemistry (in terms of people diversity, not molecules). This session originated 4 years ago with a focus on ‘Women in Chemistry’, but every year the discussions raised more issues than time allowed. We’re broadening the topics but breaking them into smaller discussion-focused groups; topics will include (with more details coming in February):

Paternity and Extended Leave Moderator(s): Thomas Garner, Genentech

Advancing Women in Chemistry Moderator(s): Katerina Leftheris, Vilya

Diversity, Equity, and Inclusion Efforts at Institutions & Companies Moderator(s): Michelle Arkin, UCSF

PLENARY KEYNOTE SESSION

8:30 Plenary Welcome Remarks from Lead Content Director with Poster Finalists Announced

Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

8:35 PLENARY KEYNOTE: Reimagining Druggability Using Chemoproteomic Platforms

Daniel Nomura, PhD, Professor of Chemical Biology and Molecular Therapeutics, Department of Chemistry, University of California, Berkeley

One of the greatest challenges that we face in discovering new disease therapies is that most proteins are considered “undruggable,” in that most proteins do not possess known binding pockets or “ligandable hotspots” that small molecules can bind to modulate protein function. Our research group addresses this challenge by applying chemoproteomic platforms to discover and pharmacologically target unique and novel ligandable hotspots for disease therapy.

9:20 Coffee Break in the Exhibit Hall with Poster Viewing and Best of Show Awards Announced

PPI-TARGETING TOOLS AND INNOVATIONS

10:10 Chairperson’s Remarks

Heike Wobst, PhD, Senior Scientist, Jnana Therapeutics

10:15 Targeted Autophagy for Degradation of Aberrant PPI Complexes

Chang Hoon Ji, PhD, Executive Director, Bio R&D Center, AUTOTAC Bio, Inc.

Protein-Protein Interactions

Small Molecule Lead Discovery and Optimization for Difficult Drug Targets

Protein complexes and many non-protein targets are degraded in the lysosome via autophagy. This is in contrast to the ubiquitin proteosome system which is the 'final' destination of proteins. I describe our targeted protein degradation platform for lysosome: the AUTOphagy-TArgeting Chimera (AUTOTAC) TPD platform was used to selectively degrade pathological aggregates, and combat neurodegeneration-associated pathophysiology.

10:45 Affinity Selection-Mass Spectrometry (ASMS) Applicability for PPI Targets

Hans-Peter N. Biemann, PhD, Distinguished Scientist, Integrated Drug Discovery, Sanofi

Affinity Selection-Mass Spectrometry (ASMS) identifies novel small molecule ligands for soluble and membrane proteins via a mass-encoded readout. We have recently applied ASMS to several challenging targets across different protein classes. These target proteins generally lack recognized druggable clefts and include PPI moieties. This presentation will review the process and status of hit ID comprising distinct externalized library HTS, as well as accession of Sanofi's internal collection via virtual screening.

11:15 Sponsored Presentation *(Opportunity Available)*

11:30 Proteomic Discovery of Chemical Probes that Modulate Protein Complexes in Human Cells

Jarrett R. Remsberg, PhD, formerly of Cravatt Lab, Scripps Research Institute; Scientist, Proteomics, Belharra Therapeutics

Most human proteins lack chemical probes, and while several large-scale and generalizable small-molecule binding assays have been introduced, how compounds discovered in "binding-first" assays affect protein function often remains unclear. Here, we describe a "function-first" proteomic strategy that uses size exclusion chromatography (SEC) in conjunction with cysteine-directed activity-based protein profiling to identify changes in protein-protein interactions, including stereoselective engagement of SF3B1, stabilizing a dynamic state of the spliceosome.

12:00 pm Inducing Conformational Change: Could AI Have Discovered this PPI Inhibitor?

Jonathan B. Baell, PhD, Executive Director, Early Leads Chemistry, Lyterian Therapeutics

Peptidomimetic design to mimic protein-protein interaction hotspot is a logical approach to PPI inhibitor discovery. We had done so for the BCL-XL -BH3 binding groove by mimicking important BH3 protein binding residues. Unexpectedly, more optimized ligands induced an entirely unexpected conformation of BCL-XL. In light of the current AI debate, we revisit this observation as a challenging benchmark to which AI-enabled PPI discovery should aspire.

12:30 Transition to Lunch

12:35 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

1:05 Refreshment Break in the Exhibit Hall with Poster Awards Announced *(Sponsorship Opportunity Available)*

ALLOSTERIC MODULATORS

1:55 Chairperson's Remarks

Robert D. Mazzola, PhD, Director & Principal Scientist, Chemical Research, Merck & Co.

2:00 Fragment-Based Discovery of Allosteric SHP2 Inhibitors

Tom Davies, PhD, Director, Molecular Sciences, Astex Pharmaceuticals

We present the application of FBDD to the oncology target SHP2 phosphatase. Hits at an allosteric site were evolved using structure-based design to a low-nanomolar lead which inhibits tumour growth in xenografts. Phosphatases have been deemed undruggable due to their polar and conserved active sites, and we highlight the ability of fragment-based screening to detect hits in novel pockets which can be exploited to identify differentiated modulators for challenging targets.

2:30 Targeting CBM, a Tri-Protein Signaling Hub, by Inhibition of MALT1 for the Treatment of B Cell Lymphomas

Murali Ramachandra, PhD, CEO, Aurigene Discovery Technologies, Ltd.

MALT1 is a key regulator of antigen-receptor signaling, wherein it partners with BCL10 and CARMA1 to form the CBM complex in which protease activity of MALT1 cleaves the negative regulators leading to activation of NF-kB. Constitutive activation of NF-kB is a key driver in B cell lymphomas. We have identified a development candidate that inhibits MALT1 with the "best-in-class" profile including potent activity in whole blood and selectivity over off-targets.

3:00 PLENARY PANEL DISCUSSION: Innovative Drug Discovery: Insights from Venture Capitalists

Co-Moderators:
Michelle Arkin, PhD, Chair and Distinguished Professor, Pharmaceutical Chemistry & Director, Small Molecule Discovery Center, University of California, San Francisco
Daniel A. Erlanson, PhD, Senior Vice President, Innovation and Discovery, Frontier Medicines Corporation

The high-risk but 'high impact-when-successful' strategy of VC investors gives them a uniquely critical lens through which to view innovation. Join us for an interactive discussion with VCs who will share the trends they are watching in drug discovery. The panel represents a variety of small and large venture firms, who provide early rounds of funding, as well as, those who invest at later or all stages.

Panelists:
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Rebecca Silberman, PhD, Senior Venture Associate, RA Capital Management LLC
Shyam Masrani, Principal, Medicxi
Jamie Kasuboski, PhD, Vice President, OMX Ventures
Olga Danilchanka, PhD, Principal, MRL Ventures Fund

3:45 Networking Refreshment Break

TARGETED COVALENT INHIBITORS

4:00 Covalent Discovery at AstraZeneca: Delivering the Next Generation of Irreversible Medicines

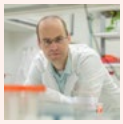
Henry Blackwell, PhD, Senior Scientist, Medicinal Chemistry, AstraZeneca

The rational search for covalent drugs has typically relied on the development of potent reversible binders, followed by the appending of an electrophilic warhead. Recently, a distinct approach involving the screening of covalent fragment-sized molecules has proved to be a viable method for the discovery of hits against previously intractable targets, including PPIs. This talk describes how AstraZeneca are pioneering the use of the electrophile-first approach for covalent drug discovery.

4:30 Small Molecule-Targeted Covalent Inhibitors of the HEG1-KRIT1 Protein-Protein Interaction

Carlo Ballatore, PhD, Professor, Pharmaceutical Science, University of California San Diego

Protein-protein interaction (PPI) between HEG1 (Heart of glass 1) and KRIT1 (Krev interaction trapped 1) plays an important role in controlling vascular development and permeability. I report the identification/characterization of hydroxy-naphthaldehyde (HNA) fragments that act as targeted covalent reversible ligands of a noncatalytic Lys of KRIT1 with high specificity and long residence time (>8h) resulting in inhibition of the PPI in cell-free and cell-based assays: potential therapeutics and/or pharmacological tools.



5:00 FEATURED PRESENTATION: Lysine-Targeted Covalent Protein Reagents

Nir London, PhD, Senior Scientist, Organic Chemistry, Weizmann Institute of Science

Installing a covalent electrophile on a peptide or protein-based scaffold with an extended binding footprint enables the targeting of shallow protein surfaces not typically addressable using small molecules. We report protein-based thio-methacrylate esters: electrophiles with a diverse reactivity profile that can be installed easily on unprotected peptides and proteins via cysteine side chains, and react efficiently and selectively with cysteine and lysine side chains on the target.

5:30 Close of Conference

AI/Machine Learning for Early Drug Discovery - Part 2

Generative AI & Predictive Algorithms for Small Molecule & Peptide Therapeutics

WEDNESDAY, APRIL 3

12:00 pm Registration Open

1:30 Welcome Remarks

AI FOR ADME/Tox PREDICTIONS

1:35 Chairperson's Remarks
Sean Ekins, PhD, Founder & CEO, Collaborations Pharmaceuticals, Inc.

1:40 *In silico* ADME/Tox in the Generative AI Paradigm
Sean Ekins, PhD, Founder & CEO, Collaborations Pharmaceuticals, Inc.
In the early 2000s pharmaceutical drug discovery was beginning to use computational approaches for ADME/Tox prediction in an effort to reduce the risk of later stage failures. Much has been written in the intervening twenty-plus years and significant expenditure has occurred in companies developing these *in silico* capabilities. It is therefore an appropriate time to assess where these tools can fit in today's generative AI paradigm for drug discovery.

2:10 Modeling Industrial ADME Datasets Using Multitask Neural Networks
Joe Napoli, PhD, Principal AI Scientist, DMPK, Genentech Inc.
Significant quantities of ADME data are collected throughout early discovery to inform molecular designs and mitigate risk. Quantitative structure-property relationship (QSPR) models aim to extract maximal value from these datasets by learning relationships between molecular structures and the ADME properties of interest. We present findings from a study focused on modeling historical ADME datasets with multitask neural networks, using both fully internal datasets as well as hybrid internal/external datasets.

2:40 Sponsored Presentation *(Opportunity Available)*

3:10 Refreshment & Dessert Break in the Exhibit Hall with Poster Viewing

AI-ENABLED PIPELINE PROGRESSION

4:00 Recursion Map-Based Drug Discovery Approach: From Project Ideation to Lead Optimization
Lourdes Rueda, PhD, Principal Scientist, Medicinal Chemistry, Recursion Pharmaceuticals Inc.
Recursion's integrated operating system combines proprietary in-house data generation and advanced computational tools to generate novel insights to initiate and accelerate programs. Using our platform we follow a *mapping and navigating* approach that enables us not only to unravel the complexity of biology but also to identify chemical starting-points and drive SAR. Following this novel approach we efficiently advance projects from initiation through different stages of pre-clinical development.

4:30 Leveraging ML and Mechanistic Modeling in Concert to Accelerate Drug Discovery
Garegin Papoian, PhD, Monroe Martin Professor of Chemistry & Biochemistry, University of Maryland Institute for Physical Science and Technology
In silico modeling has aided drug development but remains handicapped by speed/throughput and predictability of properties that lead to drug success. We're combining both physics-based modeling and machine learning to create an end-to-end drug discovery pipeline comprising generation and filtering of new chemical entities for a target in days. Our tools have outperformed other publicly-known tools on benchmarks and have successfully identified true binders from false positives for JAK2.

5:00 In-Person Breakouts

5:45 Close of Day

5:45 Dinner Short Course Registration

6:15 Dinner Short Courses*
*Premium Pricing or separate registration required. See Short Courses page for details.

THURSDAY, APRIL 4

7:15 am Registration Open

7:45 Diversity in Chemistry Breakfast Discussion *(Sponsorship Opportunity Available)*
Grab a plate and then a seat to join one of the discussions below on growing the enterprise of chemistry (in terms of people diversity, not molecules). This session originated 4 years ago with a focus on 'Women in Chemistry', but every year the discussions raised more issues than time allowed. We're broadening the topics but breaking them into smaller discussion-focused groups; topics will include (with more details coming in February):
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PLENARY KEYNOTE SESSION

8:30 Plenary Welcome Remarks from Lead Content Director with Poster Finalists Announced
Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

8:35 PLENARY KEYNOTE: Reimagining Druggability Using Chemoproteomic Platforms
Daniel Nomura, PhD, Professor of Chemical Biology and Molecular Therapeutics, Department of Chemistry, University of California, Berkeley
One of the greatest challenges that we face in discovering new disease therapies is that most proteins are considered "undruggable," in that most proteins do not possess known binding pockets or "ligandable hotspots" that small molecules can bind to modulate protein function. Our research group addresses this challenge by applying chemoproteomic platforms to discover and pharmacologically target unique and novel ligandable hotspots for disease therapy.

9:20 Coffee Break in the Exhibit Hall with Poster Viewing and Best of Show Awards Announced

AI FOR HIT-TO-LEAD OPTIMIZATION

10:10 Chairperson's Remarks
Steve Swann, PhD, CSO, Chemistry & Design, TandemAI

10:15 Optimizing Lead Series for Two Targets by Fusing AI and Physics-Based Simulations
Steve Swann, PhD, CSO, Chemistry & Design, TandemAI
This will talk will describe the use of active learning and FEP to optimize chemical series on 2 active drug discovery programs. Using generative design we are able to generate a large set of analogs for any chemical series, and identify the highest probability ideas using FEP and ML ADME models. This approach is the first to combine AI and established structure-based methods to accelerate optimization of a chemical series.

AI/Machine Learning for Early Drug Discovery - Part 2

Generative AI & Predictive Algorithms for Small Molecule & Peptide Therapeutics

10:45 Discovery of HRO761, an Allosteric, First-in-Class Clinical WRN Inhibitor, Demonstrating Synthetic Lethality in MSI Cancers

Henrik Moebitz, PhD, Investigator III, Oncology & Exploratory Chemistry, Novartis Institutes for Biomedical Research

We used a digital assay and generative chemistry to improve the physicochemical properties of our beyond-rule-of-5 lead, increasing oral exposure by a million-fold. The clinical WRN inhibitor HRO761 has the best physico-chemical profile of all *de novo* designed oral drugs above 700 Da, resulting in excellent human pharmacokinetics.

11:15 Sponsored Presentation *(Opportunity Available)*

11:30 Optimized Molecules for Optimized Profiles: An AI-Driven Platform for Small Molecule Drug Discovery

Fred Manby, DPhil, Co-Founder & CTO, Iambic Therapeutics

Iambic has created a cutting-edge AI-driven platform to tackle the most challenging design problems in drug discovery and address unmet patient need. Our platform enables us to widely explore chemical space, while also sampling a wide range of target product profiles. We have demonstrated our platform on initial programs, with our first scheduled for clinical entry just two years after launch.

12:00 pm Identifying Hit and Lead Optimization Using Medicinal Chemistry-Centric Explainable AI Platform

Sung Jin Cho, PhD, CEO, CIMPLRX

Traditional drug discovery platforms, developed by technical experts, often lack user-friendly designs and the expertise of medicinal chemists. CEEK-CURE, a novel medicinal chemistry-centric explainable AI (XAI) platform, bridges this gap. In this presentation, we will demonstrate the transformative impact of a medicinal chemistry-centric AI platform on enhancing hit rates and selectivity profiles. We will showcase two different projects focusing on oncology and neuropathic pain targets.

12:30 Transition to Lunch

12:35 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

1:05 Refreshment Break in the Exhibit Hall with Poster Awards Announced *(Sponsorship Opportunity Available)*

AI/ML FOR TARGET-SPECIFIC APPLICATIONS

1:55 Chairperson's Remarks

Lourdes Rueda, PhD, Principal Scientist, Medicinal Chemistry, Recursion Pharmaceuticals Inc.

2:00 AI-ML Docking Pipeline for Giga-Screens versus New Target Profiles and Hidden Pockets

Ruben Abagyan, PhD, Professor, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego

Rapidly evolving computer hardware, software, and machine learning algorithms, rapidly growing databases related to chemical compounds, biomolecules and biomedicine offer a unique opportunity to accelerate lead discovery for unmet medical needs, rare/neglected diseases, and emerging threats. We will describe the recent advances in searching billions of compounds for challenging tasks and new targets by combining large-scale docking, modeling, GPU-algorithms, with AI and machine learning in one pipeline.

2:30 Prospective Design of a Selective Cyclin E/CDK2 Dual Degrader

Bryce Allen, PhD, Co-Founder & CEO, Differentiated Therapeutics

With the surge in targeted protein degradation as a therapeutic strategy, there is an increasing demand for novel molecules capable of selectively targeting and degrading disease-associated proteins. Cyclin E and CDK2, key regulators of the cell cycle, have been implicated in various malignancies and represent promising therapeutic targets. We describe the prospective design of degrader molecules with high specificity for Cyclin E and CDK2 enabled by the Auto/dx platform.

3:00 PLENARY PANEL DISCUSSION: Innovative Drug Discovery: Insights from Venture Capitalists

Co-Moderators:
Michelle Arkin, PhD, Chair and Distinguished Professor, Pharmaceutical Chemistry & Director, Small Molecule Discovery Center, University of California, San Francisco
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Jamie Kasuboski, PhD, Vice President, OMX Ventures
Olga Danilchanka, PhD, Principal, MRL Ventures Fund

3:45 Networking Refreshment Break

4:00 Using AI in RNA-Small Molecule Drug Discovery

Timothy Allen, PhD, Head of ChemAI, Serna Bio

At Serna Bio, we're investigating the potential of AI to rapidly accelerate the discovery and development of small molecule modulators of RNA function. To train our ML models, we've generated a proprietary dataset of ~2.5 million RNA-small molecule binding data points. Using these models, we can computationally learn features of small molecules that bind to different RNA motifs and identify distinct chemical features in different subsets of RNA binders.

4:30 Unlocking the Druggable Universe of 3D RNA Structures with AI

Stephan Eismann, PhD, Founding Scientist & Machine Learning Lead, Machine Learning & Engineering, Atomic AI

Since our inception, Atomic AI has made substantial advances to PARSE, our Platform for AI-driven RNA Structure Exploration, which can predict 3D structures of disease-relevant RNA targets at unprecedented speed and accuracy. Among other things, PARSE allows us to identify and target RNA related to diseases that were once deemed undruggable.

5:00 Transfer-Learning for Drug Discovery: Focus Is All You Need

Anton Filikov, PhD, Associate Director, Computational Drug Discovery, Arrakis Therapeutics

Transfer-learning is gaining popularity in AI for drug discovery. In this framework, pre-training on related tasks on a large assistant dataset may yield predictive performance gains on the primary task. The magnitude of these gains hinges on the relevancy of the assistant dataset. We have explored different assistant datasets/tasks for ChemBERTa and HiGNN model architectures. We will discuss the utility of this approach and lessons learned.

5:30 Close of Conference

Oral Peptides & Macrocyclics

bRo5 Yet Drug-Like Molecules

WEDNESDAY, APRIL 3

12:00 pm Registration Open

1:30 Welcome Remarks

ENCODED LIBRARIES AND MACHINE LEARNING FOR MACROCYCLIC SCREENING

1:35 Chairperson's Remarks
Chengzao Sun, PhD, Principal Scientist, Janssen Pharmaceuticals Inc

1:40 High-Throughput Encoded Peptide Discovery for Challenging Targets via mRNA Display
Christopher Stratton, PhD, Senior Scientist, Discovery Technologies & Molecular Pharmacology, Janssen Pharmaceuticals, Inc.
Advances in target deconvolution have offered an increasing number of disease-relevant interactions that are difficult to address with traditional small- or large-molecule drugs. Peptides constitute a middle ground that provide large, yet synthetically accessible scaffolds, with the potential for oral delivery. This talk will cover the application of mRNA display to high-throughput peptide screening and the integration of this technology at J&J to enable lead discovery for challenging targets.

2:10 DNA-Encoded Macrocyclic Libraries: Design and Case Study
Jack D. Scott, PhD, Director, Discovery Chemistry, Merck & Co.
Macrocyclic peptides are a modality of high interest to the pharmaceutical industry as a way to inhibit protein-protein interactions. In recent years, DNA-encoded libraries (DEL) have been utilized to generate macrocyclic libraries utilizing non-canonical amino acids with a wide variety of ring-closing chemistries. This talk will describe our efforts to design and produce a novel macrocyclic DEL and highlight a case study using this DEL.

2:40 Sponsored Presentation *(Opportunity Available)*

3:10 Refreshment & Dessert Break in the Exhibit Hall with Poster Viewing

4:00 Structure Prediction of Cyclic Peptides via Molecular Dynamics and Machine Learning
Yu-Shan Lin, PhD, Associate Professor, Chemistry, Tufts University
A major obstacle to cyclic peptide development is that little structural information is available, as most cyclic peptides adopt multiple conformations in solution. By combining molecular dynamics simulation and machine learning, we can now provide simulation-quality cyclic peptide structure predictions in seconds to enable structure-based design of cyclic peptides and an understanding of their sequence-activity relationships.

4:30 Unlocking the Potential of Explainable AI in Designing Functional Peptide Libraries
Andrew Chang, PhD, CEO, DeepSeq.AI
In this talk, we will delve into the integration of yeast surface display and explainable AI in crafting next-generation peptide scaffold libraries. These libraries are optimized for efficient, proper folding. Panning trials with these libraries have yielded peptides with enhanced stability and folding properties, marking a significant advancement in peptide therapeutics.

5:00 In-Person Breakouts

5:45 Close of Day

5:45 Dinner Short Course Registration

6:15 Dinner Short Courses*
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THURSDAY, APRIL 4

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9:20 Coffee Break in the Exhibit Hall with Poster Viewing and Best of Show Awards Announced

TOWARDS MEMBRANE PERMEABILITY FOR BEYOND RULE OF FIVE (bRo5) MOLECULES

10:10 Chairperson's Remarks
Hao Wu, PhD, Scientist 4, Genentech Inc.

10:15 FEATURED PRESENTATION: Screening for Permeable Macrocyclic Peptides
Emel Adaligil, PhD, Senior Scientific Manager, Peptide Therapeutics, Genentech, Inc.
Developing cell-permeable macrocyclic peptides is still a big challenge in the field, but we can combine macrocyclic discovery efforts from mRNA display with NMR studies and computational tools to get more cell-permeable peptides for the interest of targets. This talk combines NMR, computational studies, and mRNA display selections of macrocyclic peptides to discover more permeable peptides.

10:45 Improving Passive Membrane Permeability of Cyclic Peptides by Amide-to-Ester Substitution
Jumpei Morimoto, PhD, Lecturer, Chemistry & Biotechnology, University of Tokyo
Cyclic peptides are attracting increasing attention as therapeutic modalities. However, their low membrane permeability significantly limits their applications for drug discovery. Recently, our group has shown that amide-to-ester substitution is an effective strategy to improve the membrane permeability of cyclic peptides. In this presentation, I will discuss the effect of amide-to-ester substitution on membrane permeability and conformational dynamics of cyclic peptides.

11:15 Sponsored Presentation *(Opportunity Available)*

11:30 Traversing Cellular Barriers Beyond the Rule of Five
Robin L. Polt, PhD, Professor, Chemistry & Biochemistry, University of Arizona
I present cyclic glycosides related to endomorphin 1 and oxytocin that upon peripheral administration, effectively target their receptors in the CNS. Cyclization of linear peptides enhances serum stability *in vivo* and the cyclic nature of the peptides provides useful pharmacophores for advancement to the clinic. I will demonstrate how the degree of glycosylation affects biodistribution and BBB penetration, enhancing the promise of endogenous peptide hormones and neurotransmitters as lead compounds.

12:00 pm Mimicry of Interface Loops and Helices: An Alternate Stapled Peptide Method
Kevin Burgess, PhD, Gradipore Chair of Chemistry, Texas A&M University
Loops and helices frequently occur at protein-protein interfaces. I present a new approach to design helical mimics of PPIs. Because loops are more diverse than helices, my method mimics interface loops containing several hot spots. I'll present validation of this dual capping strategy on PPIs of medicinal value. The organic fragment of these macrocycles is smaller and more diverse than those derived from RNA-encoded libraries.

12:30 Transition to Lunch

12:35 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

1:05 Refreshment Break in the Exhibit Hall with Poster Awards Announced *(Sponsorship Opportunity Available)*

MACROCYCLIC & CONSTRAINED PEPTIDE CASE STUDIES

1:55 Chairperson's Remarks
Katerina Leftheris, PhD, Chief Scientific Officer, Vilya Therapeutics

2:00 Identification of VEGF Antagonists for Retinal Angiogenesis Inhibition through Evolution of Disulfide Constrained Peptides (DCPs)
Xinxin Gao, PhD, Principal Scientific Manager, Peptide Therapeutics, Genentech, Inc.
Disulfide constrained peptides (DCPs) are characterized by conserved cysteine residues that form intramolecular disulfide bonds. We designed and generated DCP phage libraries with enriched molecular diversity to enable the discovery of ligands against proteins of interest. Using these libraries, we identified highly specific antagonists with super affinity to vascular endothelial growth factor (VEGF), the primary driver for wet AMD. This new modality enables the discovery of next-generation ocular therapeutics.

2:30 PDL-1 Macrocyclic Inhibitor
Paul M. Scola, PhD, Group Director, Drug Discovery, Bristol Myers Squibb Co.
A macrocyclic peptide was identified as an inhibitor of PD-L1 through an *in vitro* selection process. A co-crystal structure of this macrocycle with PD-L1 enabled rapid optimization of this series with respect to PD-L1 inhibitory activity, while also providing insight as to strategies to mitigate off-target liabilities, ultimately yielding BMS-986189. This lead macrocycle progressed to the clinic, where PK/PD was evaluated in normal healthy volunteers. I discuss the discovery details.

3:00 PLENARY PANEL DISCUSSION: Innovative Drug Discovery: Insights from Venture Capitalists
Co-Moderators:
Michelle Arkin, PhD, Chair and Distinguished Professor, Pharmaceutical Chemistry & Director, Small Molecule Discovery Center, University of California, San Francisco
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Olga Danilchanka, PhD, Principal, MRL Ventures Fund

3:45 Networking Refreshment Break

4:00 FEATURED PRESENTATION: Discovery of an Orally Bioavailable Cyclic Peptide RAS Inhibitor Guided by Drug-Like Criteria
Atsushi Ohta, PhD, Head of Modality Technology Department, Chugai Pharmaceutical Co., Ltd.
Establishing a technological platform for creating cyclic peptides penetrating cell membranes and inhibiting protein-protein interactions can open the door to many valuable drugs. We have validated a new methodology by identifying several governing factors for cyclic peptides to be drug-like and developing library technologies affording highly N-alkylated cyclic peptide hits. As the first example of this technology, the discovery of a RAS inhibitory clinical compound (LUNA18) will be presented.

4:30 Expansive Discovery of Chemically Diverse Structured Macrocyclic Oligoamides
Patrick J. Salveson, PhD, Co-Founder and Vice President, Research & Development, Vilya Therapeutics
Here we will describe a general computational method for identifying closed macrocycles composed of combinations of alpha, beta, gamma, and 17 other amino acids classes with distinct backbone chemistries. The method enables atomically accurate *de novo* design of permeable macrocycles composed of combinations of canonical and non-canonical backbones. We show using this methodology to develop selective and potent inhibitors of three protein targets.

5:00 Designing Synthetic Membrane-Active Macrocyclics as Antibacterial Agents
Keykavous Parang, PhD, Professor, Biomedical and Pharmaceutical Sciences, Chapman University
This study focused on creating potent, small cationic peptides with enhanced bacterial membrane selectivity. Synthesized cyclic peptides exhibited strong activity against drug-resistant Gram-positive (MIC=1.5-6.2 µg/mL) and Gram-negative (MIC=12.5-25 µg/mL) bacteria. When combined with antibiotics, they displayed significant synergistic effects against resistant pathogens. Cytotoxicity assays revealed higher specificity for bacteria over mammalian cells. *In vivo* experiments using a mouse MRSA septicemia model demonstrated promising pharmacokinetics and efficacy for the lead peptide.

5:30 Close of Conference

RNA-Modulating Small Molecule Drugs

Novel Approaches to Target RNA Structure, Binding, Interactions, and Function

WEDNESDAY, APRIL 3

12:00 pm Registration Open

1:30 Welcome Remarks

NEW FUNCTIONAL & SCREENING ASSAYS

1:35 Chairperson's Remarks

Amanda Garner, PhD, Associate Professor, College of Pharmacy, Department of Medicinal Chemistry, University of Michigan

1:40 Enabling Technologies for Revealing Druggable Paths in RNA Biology

Amanda Garner, PhD, Associate Professor, College of Pharmacy, Department of Medicinal Chemistry, University of Michigan

Over the past decades, we have witnessed an explosion in discoveries connecting RNAs with human diseases. Consequently, the targeting of RNAs, and more broadly, RNA biology, has emerged as an untapped area of drug discovery. In this lecture, I will discuss methods developed by the Garner Lab for exploring the druggability of cellular RNAs and RNA-protein interactions.

2:10 Chemical Tools for RNA Structure and Druggability

Willem Velema, PhD, Assistant Professor, Physical Organic Chemistry, Radboud University

RNA is a versatile molecule and exhibits many diverse functions. Our lab explores approaches and chemistries to study RNA structure and druggability. Using customized affinity-based profiling tools, we study RNA structural folding and small molecule ligand binding. Applying these tools to structured RNA, we determine ligand binding sites with single nucleotide resolution. Lastly, combining our tools with qPCR allows us to measure binding of RNA targeting drugs in live cells.

2:40 AI-Enabled RNA-Small Molecule Drug Discovery: What Drives Functional Outcomes?

Dale Wright, PhD, Director, Translational Biology, Serna Bio

Targeting RNAs and modulating their function could transform drug discovery. An estimated 85% of the ~3 billion base pairs in the human genome are transcribed into RNA, but only ~1.5% of these code for proteins. At Serna Bio we are using an AI-enabled, data-first approach to build the world's first map of the druggable transcriptome. I will discuss some of the challenges of developing and advancing target-specific programs.

3:10 Refreshment & Dessert Break in the Exhibit Hall with Poster Viewing

4:00 Tools to Measure RNA Binding Protein-RNA Defects

Eugene Yeo, PhD, MBA, Professor, Cellular and Molecular Medicine, University of California, San Diego; Founding Member, Institute for Genomic Medicine

I will discuss transcriptome-wide methods we have developed to assess defects and RNA binding protein-RNA changes in small molecule-mediated perturbation of systems.

4:30 Chemoproteomic Capture of RNA Binding Activity in Living Cells

Ken Hsu, PhD, Stephen F. and Fay Evans Martin Endowed Associate Professor, Department of Chemistry, The University of Texas at Austin

Here, we develop a photo-activatable-competition and chemoproteomic enrichment (PACCE) method for detecting thousands of cysteine sites on proteins displaying RNA-sensitive alterations in probe binding. PACCE is complementary to existing RNA interactome capture methods and enabled functional profiling of canonical RNA-binding domains as well as discovery of moonlighting RNA binding activity in the human proteome. Collectively, we introduce a chemoproteomic platform for proteome-wide quantification of protein-RNA binding activity in living cells.

5:00 In-Person Breakouts

5:45 Close of Day

5:45 Dinner Short Course Registration

6:15 Dinner Short Course*

SC7: Chemical Biology for Covalent Discovery, Phenotypic Screening, and Target Deconvolution

*Premium Pricing or separate registration required. See Short Courses page for details.

THURSDAY, APRIL 4

7:15 am Registration Open

7:45 Diversity in Chemistry Breakfast Discussion *(Sponsorship Opportunity Available)*

Grab a plate and then a seat to join one of the discussions below on growing the enterprise of chemistry (in terms of people diversity, not molecules). This session originated 4 years ago with a focus on 'Women in Chemistry', but every year the discussions raised more issues than time allowed. We're broadening the topics but breaking them into smaller discussion-focused groups; topics will include (with more details coming in February):

Paternity and Extended Leave Moderator(s): Thomas Garner, Genentech
Advancing Women in Chemistry Moderator(s): Katerina Leftheris, Vilya
Diversity, Equity, and Inclusion Efforts at Institutions & Companies Moderator(s): Michelle Arkin, UCSF

PLENARY KEYNOTE SESSION

8:30 Plenary Welcome Remarks from Lead Content Director with Poster Finalists Announced

Anjani Shah, PhD, Senior Conference Director, Cambridge Healthtech Institute

8:35 PLENARY KEYNOTE: Reimagining Druggability Using Chemoproteomic Platforms

Daniel Nomura, PhD, Professor of Chemical Biology and Molecular Therapeutics, Department of Chemistry, University of California, Berkeley

One of the greatest challenges that we face in discovering new disease therapies is that most proteins are considered "undruggable," in that most proteins do not possess known binding pockets or "ligandable hotspots" that small molecules can bind to modulate protein function. Our research group addresses this challenge by applying chemoproteomic platforms to discover and pharmacologically target unique and novel ligandable hotspots for disease therapy.

9:20 Coffee Break in the Exhibit Hall with Poster Viewing and Best of Show Awards Announced

EMERGING SMALL-MOLECULE MODULATORS OF RNA

10:10 Chairperson's Remarks

Thomas Hermann, PhD, Professor, Department of Chemistry & Biochemistry, University of California, San Diego

10:15 Small-Molecule Splicing Modifiers: Pharmaceutical Properties to Preclinical Efficacy

Jana Narasimhan, PhD, Associate Director, PTC Therapeutics Inc.

Small-molecule splicing modifiers to regulate protein expression have emerged as a successful strategy to address certain diseases. Diseases such as spinal muscular atrophy, familial dysautonomia, and Huntington's disease can

be targeted by small-molecule splicing modifiers. The correlation between pharmaceutical properties and pharmacokinetics, pharmacokinetics and pharmacodynamics, and between pharmacodynamics and efficacy will be discussed for select indications.

10:45 Recent Advances in the Discovery of RNA-Targeted Small Molecules

Karthik Iyer, PhD, Associate Director, Chemical Sciences, Arrakis Therapeutics

Our mission at Arrakis is to solve very broadly the problem of how to drug RNA with small molecules. This presentation will provide an update on the platform we have built to achieve that mission and provide early data on specific mRNA targets.

11:15 Sponsored Presentation *(Opportunity Available)*

11:30 The Next Generation of RNA Therapeutics for Age-Related Diseases

Rafael Bottos, Co-Founder & CEO, Aptah Bio Inc.

The Aptah platform comprises a new class of molecules capable of interacting in an innovative and versatile manner with both multiple proteins and pre-messenger RNAs. As age-related diseases remain without effective treatments, our technology offers a potential solution to target the underlying pathophysiological mechanism of several diseases, revolutionizing interventions and bringing hope to patients worldwide.

12:00 pm PANEL DISCUSSION: Addressing Challenges in Developing RNA Targeting Small-Molecule Drugs

Moderator: Thomas Hermann, PhD, Professor, Department of Chemistry & Biochemistry, University of California, San Diego
Panelists:
Rafael Bottos, Co-Founder & CEO, Aptah Bio Inc.
Gal Gur, PhD, VP, Business Development, Anima Biotech
Karthik Iyer, PhD, Associate Director, Chemical Sciences, Arrakis Therapeutics
Rabia Khan, PhD, MBA, CEO, Serna Bio
Jana Narasimhan, PhD, Associate Director, PTC Therapeutics Inc.

12:30 Transition to Lunch

12:35 Luncheon Presentation *(Sponsorship Opportunity Available)* **or Enjoy Lunch on Your Own**

1:05 Refreshment Break in the Exhibit Hall with Poster Awards Announced *(Sponsorship Opportunity Available)*

NOVEL RNA-TARGETING APPROACHES

1:55 Chairperson's Remarks

Udo Oppermann, PhD, Professor & Chair, Musculoskeletal Sciences, University of Oxford

2:00 Proximity-Induced Nucleic Acid Degrader (PINAD) Approach to Targeted RNA-Degradation Using Small Molecules

Gonçalo Bernardes, PhD, Professor, Department of Chemistry, University of Cambridge

This talk will cover recent examples on the development of click-degraders, small molecules that when in proximity can degrade RNA, akin to ribonucleases. Using click-degraders we developed meCLICK-Seq, a powerful method for the study of diverse aspects of cellular RNA methylation. We also developed proximity-driven small molecule RNA degraders to target and degrade SARS-CoV-2 genomes and exert an antiviral effect in disease models.

2:30 Development of RNA-Degrading Chimeras Targeting Viral Genomes

Jingxin Wang, PhD, Assistant Professor, Department of Medicinal Chemistry, University of Kansas, Lawrence

RNA viruses such as SARS-CoV-2 have highly structured untranslated regions (UTRs), which are vital for viral propagation. These RNA structures are promising antiviral targets. We developed a new class of molecules that target the four-way junction RNA structure named SL5 in the 5' UTR of the SARS-CoV-2 genome. We optimized the SL5-binding ligand, conjugated it to ribonuclease-recruiting moieties to create active RNA-degrading chimeras, and demonstrated their activities in SARS-CoV-2-infected cells.

3:00 PLENARY PANEL DISCUSSION: Innovative Drug Discovery: Insights from Venture Capitalists

Co-Moderators:
Michelle Arkin, PhD, Chair and Distinguished Professor, Pharmaceutical Chemistry & Director, Small Molecule Discovery Center, University of California, San Francisco
Daniel A. Erlanson, PhD, Senior Vice President, Innovation and Discovery, Frontier Medicines Corporation

The high-risk but 'high impact-when-successful' strategy of VC investors gives them a uniquely critical lens through which to view innovation. Join us for an interactive discussion with VCs who will share the trends they are watching in drug discovery. The panel represents a variety of small and large venture firms, who provide early rounds of funding, as well as, those who invest at later or all stages.

Panelists:
Wendy B. Young, PhD, BioPharma Discovery
Rebecca Silberman, PhD, Senior Venture Associate, RA Capital Management LLC
Shyam Masrani, Principal, Medicxi
Jamie Kasuboski, PhD, Vice President, OMX Ventures
Olga Danilchanka, PhD, Principal, MRL Ventures Fund

3:45 Networking Refreshment Break

4:00 Identification of tRNA Synthetases as Therapeutic Vulnerabilities in Human Cancers

Udo Oppermann, PhD, Professor & Chair, Musculoskeletal Sciences, University of Oxford

Modulating RNA functions emerges as an attractive therapeutic modality in several disease areas. By deploying chemogenomic tools, we identify and validate preclinically human prolyl-tRNA synthetase as a novel target in haematological and solid cancers. Inhibition leads to dose-dependent down-regulation of proline-rich oncogenic transcription factors and signaling molecules with concomitant cancer cell death, reduction in tumor burden, and increased host survival in *ex vivo* and *in vivo* systems.

4:30 Degrading an RNA-binding Protein to Treat BRAF-mutant Colorectal Cancer

Yong Cang, PhD, Professor, ShanghaiTech University; Co-founder & CSO, Degron Therapeutics

We performed proteomic studies on cells treated with rationally designed CRBN modulators and identified novel molecular glue degraders of a previously "undruggable" RNA binding oncoprotein (RBP). RBP controls the levels of BRAF and EGFR, and its targeted degradation inhibited BRAF-mutant colorectal cancer cell proliferation and tumor growth, either alone or synergistically with BRAF inhibitors.

5:00 High Specificity RNA-Directed Therapy for AD/PD with Implications for Treating SARS-CoV-2

Jack Rogers, PhD, Director, Neurochemistry Laboratory, Associate Professor, Psychiatry-Neuroscience, Harvard Medical School and Massachusetts General Hospital

The Alzheimer's amyloid precursor-protein and Parkinson's alpha-synuclein were shown by our laboratory to be translationally controlled via the 5'untranslated regions of their mRNAs in neurons, via uniquely-folded iron-responsive-elements RNA stem-loops. Our new 5'UTR inhibitors limited APP-amyloid and alphasynuclein in the nanomolar range to prevent formation of toxic fibrils in mouse models of PD. We unexpectedly discovered these RNA inhibitors can be repurposed to inhibit translation of the replicase in SARS-CoV-2.

5:30 Close of Conference

HOTEL & TRAVEL

Conference Venue and Host Hotel:
Hilton San Diego Bayfront
1 Park Boulevard
San Diego, CA 92101

Discounted Room Rate: $279
Discounted Room Rate Cut-off Date: March 5, 2024

Visit the Travel page of DrugDiscoveryChemistry.com to make your hotel reservations and for additional information

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